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FEDERALLY-SUPPORTED HUMAN NUTRITION RESEARCH UNITS:

SELECTED PAPERS FROM THE FIRST ANNUAL CONFERENCE

December 16-17, 1982

AN INFORMATION EXCHANGE ACTIVITY OF THE
JOINT SUBCOMMITTEE ON HUMAN NUTRITION RESEARCH

Prepared by the

Joint Subcommittee on Human Nutrition Research
of the Committee on Health and Medicine
and the Committee on Food, Agriculture, and Forestry Research
Federal Coordinating Council on Science, Engineering, and Technology
Office of Science and Technology Policy
Executive Office of the President

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CONTENTS

FOREWORD

The First Annual Conference on Federally-Supported Human Nutrition Research Units was sponsored by the Joint Subcommittee on Human Nutrition Research (JSHNR). The purpose of the conference was to enhance information exchange of the research programs; increase coordination and collaboration among the agencies; and thereby improve planning for nutrition research at the Federal level.

Nutrition research in the Federal Government encompasses a broad spectrum of activities in the following three areas:

- o Biomedical and Behavioral Sciences
- o Food Sciences
- o Nutrition Education

Research is conducted nationally and internationally, and includes studies to improve the health of civilian and military populations, including the nutritional requirements of astronauts.

The JSHNR was uniquely qualified to sponsor such a conference since its membership included representatives and alternates from all the Federal agencies that support nutrition research, and the purpose of the Subcommittee, as stated in its charter (Appendix I), was "to increase the overall effectiveness and productivity of research efforts in nutrition."

The conference was held in response to a recommendation made by the JSHNR in its 1980 report to:

> Establish an annual meeting at which the Directors of the NIH Clinical Nutrition Research Units, the intramural laboratories of USDA, NIH, and FDA, the VA clinical nutrition and alcohol research programs, and the managers of DOD and NASA programs with nutrition research components will discuss research progress and future research needs. Such discussions should lead to increased coordination and collaboration among the intramural programs on USDA, NIH, FDA, DOC, NASA, and NSF.

The First Annual Conference of Federally-Supported Human Nutrition Research Units was held in response to this recommendation. It is hoped that the readers of these proceedings will find them as informative as those who participated in the conference.

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INTRODUCTION

The First Annual Conference of Federally-Supported Human Nutrition Research Units--An Information Exchange Activity of the Joint Subcommittee on Human Nutrition Research (JSHNR) was held on December 16-17, 1982.

The first day of the conference began with introductory remarks by the Cochairpersons, Artemis P. Simopoulos, M.D. and Mary Carter, Ph.D., followed by the keynote speaker, the Honorable George E. Brown, Jr., Chairman of the Subcommittee on Department Operations, Research and Foreign Agriculture, U.S. House of Representatives. In his keynote address, Congressman Brown said he was "somewhat surprised to learn that the components of Federal nutrition research management and planning were not in place prior to the establishment of the Joint Subcommittee." In describing his views of what constitutes a nutrition research plan, Congressman Brown said:

> A Nutrition Research Plan developed and accepted by representatives of the broad range of disciplines which encompass the science and application of nutrition would play a major role in advancing the state-of-the-art and emphasizing to policy makers and to the public the need for sustained and continuous support. The plan I envision is not intended to be a mechanism for controlling nutrition research or dictating specific research activities which should be pursued by the implementators. Rather, the plan should serve as a guide for directing and motivating research which would achieve comprehensive nutrition goals as defined by the leaders of numerous disciplines which encompass the science and application of nutrition. The plan must be sufficiently flexible to tap the creativity of individuals, maintain the integrity of the scientific process, and encourage centers of excellence.

The remainder of the morning was devoted to the USDA program in human nutrition research, which included an overview of the program and presentations of highlights of USDA research by the directors of the following five nutrition centers:

- The Western Human Nutrition Research Center at the Presidio of San Francisco, California: Its mission is to develop new methodology to assess nutritional status as well as factors leading to malnutrition and to study human nutritional requirements. A major thrust of the center is the development of methodology to assist the Food and Nutrition Service (FNS) of USDA in the assessment of the effectiveness of three major USDA/FNS programs: (1) the Food Stamp program, (2) the school feeding programs, and (3) the Women-Infant-Children program.

- The Beltsville Human Nutrition Research Center: Its mission is to define human requirements for essential nutrients through basic and applied research, and to identify foods that meet the nutritional requirements through nutrient composition research.

The research activities are organized in five laboratories addressing human nutrient requirements for the major nutrient groups (carbohydrates, lipids, proteins, energy, vitamins, and minerals) and nutrient composition research.

- The USDA Human Nutrition Research Center on Aging at Tufts University, Boston, Massachusetts: Its mission is to examine the relationship of nutrition to the aging process throughout adult life and the determination of dietary needs of elderly people. Center scientists are determining the ways in which diet and nutritional status influence the onset and progression of aging through studies with experimental animals, tissue cultures, and human subjects.

- The Children's Nutrition Research Center* at Baylor College of Medicine, Houston, Texas: Its foremost mission is the measurement of nutritional needs and the attainment of optimal nutritional status in the pregnant and lactating woman, and in the child from conception to adolescence. In order to reach this objective, emphasis has been given to the development of precise methods for the investigation of normal nutrient needs, for the determination of the relationships between nutrition and normal growth and development, and for the definition of biochemical and physiological standards for normal growth and nutritional status.

- The Grand Forks Human Nutrition Research Center: Its primary responsibility is to conduct research on the role of trace minerals in human nutrition that includes defining the consequences of inadequate intakes and of those factors that influence the bioavailability of trace minerals. The research is carried out on animal models and humans beings.

The afternoon session began with an overview of the DHHS nutrition research program. The NIH extramural program, which constitutes 90 percent of DHHS expenditures on nutrition research, was presented followed by presentations by the directors of the following seven NIH supported CNRU's:

- University of Alabama CNRU: The overall goals are to improve patient care and prevent disease, using means which include nutrition education and information exchange. Among its major activities are studies related to: malnutrition of hospital patients and its prevention; identification of the role of nutritional factors in the etiology and prevention of cancer; eating disorders, including obesity, anorexia, and bulimia; the nutritional management of patients with short bowel syndrome, and home parenteral nutrition; multiphasic screening for vitamin status assessment; and folic acid biochemistry and metabolism.

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* As the reader goes through the descriptions of the USDA centers (Tufts and Baylor), they should bear in mind that Congress specifically requested that the activities of these two centers be coordinated with the activities of NIA and NICHD, respectively.

- Medical College of Georgia: The CNRU staff conducts clinical research, education, and training, and gathers information concerning the etiology and treatment of nutrition-related disorders--predominantly cardiovascular disease--affecting the population of Georgia. Research efforts are focusing on the prevention and treatment of: (1) dietary and genetic hyperlipidemias; (2) trace mineral deficiencies; and (3) obesity. A secondary research thrust is to define the effects of specific diseases and associated stress in altering the nutritional requirements of hospitalized patients, especially of fuel, protein, and trace minerals, and to improve their nutritional therapy.

- Vanderbilt University School of Medicine: The development of this CNRU has allowed establishment of core facilities for laboratories, clinical, computer and administrative activities which can be utilized in a cohesive manner and directed toward patient care, and a mechanism to support clinical nutrition research where positive results could be directly and immediately obvious. Research activities include: rapid screening for malnutrition for hospitalized patients; nasogastric feeding at home in oat cell cancer patients; micronutrient metabolism in patients with essential fatty acid deficiency; trace elements in chronic renal disease; nutritional intervention in the moderately malnourished patient; zinc and copper requirements for infants and children requiring special nutritional support; nutritional changes in patients undergoing coronary artery bypass surgery; breast milk and micronutrients; the antibacterial effect of zinc and copper in dialysis fluid; derivation of normal values from Red Cross blood; use of an elemental diet in treatment of cystic fibrosis; plasma amino acids after intravenous administration of the test solution (F-14) and L-Cysteine-HCL to pediatric patients requiring TPN; and concentration of taurine, carnitine, and amino acids in pre-term and full-term human milk.

- Memorial Sloan-Kettering Cancer Center, New York Hospital-Cornell Medical Center, and the Rockefeller University: This units consists of an administrative core facility and five core laboratories: biophysics, immunology, lipids, mass spectrometry, and metabolism and minerals. Major areas of research include nutrition and its relationship to cancer, immunology, burns, pharmacology, and the brain; metabolism and diabetes; and lipids. Patient care and public and professional education are highly visible components of the MSKCC/Cornell/Rockefeller unit. Noted as one of the pioneer programs in the country, the Nutritional Support Service supervises in- and outpatient total parenteral nutrition (TPN) and enteral nutrition.

- University of Chicago: This unit facilitates and encourages clinical investigation of nutritional aspects of human diseases. By extending the efforts of the University's Committee on Human Nutrition and Nutritional Biology, the CNRU fosters interdisciplinary efforts in clinical nutrition research, patient care, education, and research training. A major goal is the application of current progress in laboratories and animal research to

human nutrition investigation. The CNRU consists of seven core laboratories, facilities for nutritional assessment and support, and for study design and data management, and an administrative core that also coordinates education and training activities. Ongoing research focuses on lipid metabolism and cardiovascular disease; stable isotopes/breath tests; metabolism of vitamins, minerals, and trace metals; and the interrelations of nutrition with growth, digestive disorders, and with diabetes. Patients followed by the Nutrition Support Service are the focus of additional clinical protocols that draw on assays from several of the core laboratories. The current goals are to: (1) provide expanded access to existing facilities and services for nutritional research, (2) develop new analytical and research facilities, and (3) extend nutrition education, training, and research activities.

- University of Wisconsin: This unit is actively engaged in research, education, and training, and patient care in clinical nutrition. Organization of the unit is based on three activities: administration, services and facilities, and investigators/users. Research focuses on carnitine nutriture and its potential deficiency in disease states, and carnitine therapy; the effects of nutrients and natural products on serum lipids, particularly total and high density lipoprotein (HDL) cholesterol; and the adverse effects of TPN leading to complications of fatty liver and metabolic bone disease.

- Columbia University College of Physicians and Surgeons: The unit focuses on the pediatric patient. Major areas of research encouraged and supported by the CNRU concern nutrition of low birth weight infants, metabolic effects of TPN, cholesterol turnover, and metabolic response to the stress of illness. The unit consists of three core components: the clinical core, laboratory core, and biomathematics core. The nucleus of the clinical core, which includes a team of physicians, nutritionists, nurses, and technicians, is the Nutrition Support Service at Babies Hospital (Presbyterian Hospital in New York City); additional personnel are provided by CNRU funds to ensure that nutritional support is available for research as well as for clinical needs. The laboratory core includes an amino acid laboratory, a lipid laboratory, and a general biochemistry and nutrition laboratory. The biomathematics core includes a team of biostatisticians and computer programmers who assist with study design as well as with data analyses. Computer facilities used by the team are shared by other major research groups.

The CNRU presentations were followed by a brief description of the NIH intramural program in nutrition research. We selected for presentation one particularly interesting intramural study entitled "Obesity as an Independent Risk Factor for Cardiovascular Disease: A 26-year Follow-up of Participants in the Framingham Heart Study," by Dr. Helen Hubert. The paper was subsequently published in Circulation (67:5, 968-977, May 1983), and has been reproduced in Appendix II.

Presentations by FDA staff concluded the first day of the conference. An overview of the FDA nutrition program was given, followed by the activities and goals of FDA's Division of Nutrition. The second day of the conference began with a presentation on the nutrition research activities of FDA's Division of Consumer Studies, followed by a presentation of DOD programs with nutrition research components. DOD activities include projects to improve the nutritional regimens of the military, develop more effective nutrition information delivery systems suited to the needs of the military, and detailed procedural guides for national, international, and military nutrition assessment studies.

The VA's nutrition research programs are directed against diseases affecting substantial segments of the veteran population. From the 50 Veterans Administration Medical Centers with a substantial nutrition component, five were chosen for presentation:

- o Lexington, KY: Research at this facility on plant fiber intake has shown important benefits for selected patients with metabolic disorders (diabetes, obesity, hypercholesterolemia, hypertriglyceridemia, hypertension, and hypoglycemia). Collaborative studies to delineate the mechanisms responsible for these effects and to determine the long-term effects of fiber intake on mineral balance are in progress.

- o Bronx, NY (Hematology & Nutrition and Hematopathology Laboratories: The research at these laboratories primarily involves studies of hematologic nutrition, particularly that affecting folate and vitamin B_{12} status, with respect to the food sources, absorption, transport and utilization of these vitamins and of their binding proteins. Studies on folate look at the effect of milk proteins on folate absorption, folate deficiency in adults, and congenital folate malabsorption. Radioassay studies on vitamin B_{12}, abnormal vitamin B_{12} binders in pernicious anemia, and vitamin B_{12} analogues in mammalian tissue and in foods are also being studied.

- o Bronx, NY (Laboratory of Liver Diseases & Nutrition, and Alcohol Research Center: Ongoing nutritional studies include drug and ethanol induced alterations of hepatic vitamin A and associated liver changes; and alteration of amino acid and protein metabolism in the alcoholic. Studies on Fetal Alcohol Syndrome, which is the leading preventable cause of birth defects and mental retardation, are being planned with the specific aims being to assess the effects of chronic ethanol administration on the rat pancreas under conditions of suboptimal nutrition (protein and methionine); to determine the relationship between nutritional status and pancreatic exocrine function in asymptomatic human alcoholics; and to identify alcoholics at high risk for the development of pancreatitis by the prospective, longitudinal assessment of nutritional status and pancreatic function. Because many of the ongoing and planned studies are made possible by the application of the feeding of alcohol as part of a total liquid diet, variations in this diet are being compared and three standardized basic formulas are being proposed.

- o Little Rock, AR: This program primarily studies nutritional aspects of the aging process, with particular attention on the development of appropriate standards for nutritional assessment of the elderly, documentation of the prevalence and severity of protein calorie malnutrition in homebased, institutionalized and ill elderly, the reversibility of protein calorie malnutrition, and finally the interrelationships among nutrition, age and host defense.

- o Nashville, TN: This center has no independently supported human nutrition research unit as such, rather the nutritionally related research is supported by individual merit review (VA) or by individual research grants from NIH or drug companies. A metabolic assessment laboratory supported by the CNRU serves as a resource for some of the studies. The studies are divided into either basic or clinical. Basic studies include studies on the cellular folate binding proteins, folate metabolism, and thiamin metabolism. Clinical studies include: vitamin A binding proteins in human skin tumors, studies on total parenteral nutrition, nutritional assessment of VA patients, and nutritional status of patients receiving TPN.

Presentations on AID's program and the two international centers, the International Center to Control Nutritional Anemia and the International Center for Epidemiologic and Preventative Ophthalmology, concluded the morning session. AID supports human nutrition research as part of its programs to assist less developed countries in improving the nutritional status of their populations. The goals of the AID nutrition program are to: enable the developing countries to formulate productive nutrition policies and develop effective programs, and to enable developing countries to maximize the nutritional benefits derived from related government policies and programs such as in agriculture and health.

The afternoon session began with a special presentation by Dr. Alfred E. Harper on the impact of the CNRU's on nutrition education in medical schools. In summary, Dr. Harper said that reports from the CNRU directors indicate uniformly that establishment of CNRU's has strengthened the place of nutrition in the medical curricula of the universities participating in the program. The comments received indicate that there is less fragmentation in the presentation of nutrition knowledge, an impetus for expanding nutrition offerings, an improved environment for nutrition in the medical schools and a heightened awareness of the importance of nutrition within the medical curriculum. Although it is not possible to quantify these effects, the comments would indicate that nutrition is being accepted on a basis equivalent to that of the traditional medical subjects and that it has begun to gain a stable position in the curriculum.

Dr. Harper said that besides providing evidence of an expanded place for nutrition in the medical curriculum, the reports of the CNRU directors also indicated that expanded nutrition support services as the result of establishment of CNRU's have made possible more case presentations with nutritional problems at grand rounds, more seminars on nutritional topics and more requests for guest lectures on nutritional subjects in both preclinical and clinical courses. In

several medical schools, electives have been developed on clinical aspects of nutrition in which there is involvement of fellows and residents. The development of clinical nutrition rounds has also been facilitated in several institutions by the establishment of the CNRU's.

In his concluding remarks, Dr. Harper said that, in general, the directors agreed that establishment of CNRU's has given visibility to nutrition programs, has increased opportunities for participation by medical students and fellows in research projects on nutrition problems, and has increased the awareness of faculty of the appropriateness of a place for nutrition in the management of patients. There can be little doubt that the CNRU's have contributed greatly to expanded education in nutrition in the medical schools in which they have been placed.

The remainder of the afternoon session was devoted to a discussion of program strengths and gaps, research needs, and recommendations for further coordination and planning efforts. Because of the importance of the issues raised and the excellent discussion by the participants, the transcript of this session appears at the end of the formal papers.

The first annual JSHNR conference provided the participants with first-hand information on the nutrition research priorities under way at the various federally supported human nutrition research centers, and thereby established a solid basis for a thorough and exciting exchange of nutrition research findings and priorities. One important point stressed by the Directors of the Centers as well as other participants was the interdependence of all components of the Federal nutrition research effort and the need to keep open the channels of communication in order to stimulate continuous cooperation. The participants considered this first conference an overwhelming success and expressed a desire to participate in the second annual conference.

The proceedings of this conference consist of the papers submitted by each presenter which accounts for the differences in format. No attempt was made to edit these submissions.

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KEYNOTE ADDRESS

By

Congressman George E. Brown, Jr.

KEYNOTE ADDRESS

Congressman George E. Brown, Jr.

I am pleased to participate in this First Annual Conference of Federal Human Nutrition Research Units. Since the expected outcomes of the conference are "To increase coordination and collaboration among the agencies and thereby enhance planning for nutrition research at the Federal level," I assume you do not totally disagree with the current emphasis I have urged the Science Committee and the Agriculture Committee to place on nutrition research and comprehensive planning. On the other hand, your invitation for me to speak here this morning may have resulted from concerns that the mechanisms the Committees hoped would motivate research planning and implementation are either ineffective or unnecessary. If this is the case, I especially appreciate the opportunity to be here so that we may exchange viewpoints, and I can learn from the nutrition experts assembled here today.

Let me begin by expressing my views on the role of planning in advancing the frontiers of science and technology and on the importance of several components of planning. As you well know, Congress has not demonstrated outstanding expertise in either coordination or planning. In fact, the frequently disparate Congressional directives resulting from overlapping jurisdictional boundaries of numerous Committees, and the disruption caused by budgetary uncertainty have no doubt hindered your ability to implement your own near-term goals. Unfortunately, this situation is not likely to change in the immediate future. Although that realization may neither be a surprise nor an encouragement to you, it does demonstrate the need for scientists in government, academia, and industry to jointly develop a comprehensive plan to guide research initiatives in nutrition as well as to guide policy-makers.

Dr. Simopoulos has commented on some of my Subcommittee involvement in nutrition. While the Subcommittees' jurisdictions are fragmented and irrational, the individuals on the Subcommittees tend to try to integrate these various jurisdictional conflicts into some sort of a coordinated whole. In terms of my role on both the Agriculture Committee and the Science Committee: I have served on both these Committees for many years and I have maintained and developed a continuing interest in this general problem of how to more effectively coordinate and plan for scientific research in a variety of fields. I try to address this problem in any Subcommittee that I may chair in a particular session of Congress. During this session, I chaired the Agriculture Subcommittee, dealing with Department Operations, Research, and Foreign Agriculture (DORFA). In the last session, it was the Science Committee's Subcommittee on Science, Research, and Technology (SRT), and before that, it was the Science Subcommittee now entitled the Subcommittee on Natural Resources, Agricultural Research, and the Environment.

In all of these Subcommittees, there are members who have an interest in the general health of research, and how it could be better organized. What generally results is the emergence of some kind of consensus among those Subcommittee members that there are certain things that need to be done. Generally speaking, this has led to an emphasis on developing coordinated research plans where you have research that is being conducted throughout the government which is complex, frequently multidisciplinary, and cuts

across jurisdictional boundaries. That is the generic problem that you are seeking to address with this conference today.

I am convinced that a nutrition research plan developed and accepted by representatives of the broad range of disciplines which encompass the science and the application of nutrition would play a major role in advancing the state-of-the-art and emphasizing to policy-makers and to the public the need for sustained and continuous support. You may not care about the quality of research, but I know you care about sustained support. You have to see the relationship between having a coordinated approach and sustained and continuous support. Organized and coordinated views which result from the process of planning are imperative to the development of a consensus which guides public policy and related budgetary actions.

I know that you must be familar with similar planning efforts in other research areas. For example, the coordinated toxicology program that runs across the government was developed for the same reason. And, the National Climate Program Act exists for the purpose of bringing together climate research activities, a fairly esoteric field. That Act is embodied in a special piece of legislation. There are numerous other examples of efforts to pull together a framework for similar kinds of complex programs. There is no magic solution. I cannot tell you what is the best way to develop the plan, but I can tell you that rational people perceive the need for rational guidance to these kinds of programs, and they want tools to guide them. And, those tools are the plans that you are going to be working on.

Thus, I am very pleased that Dr. Keyworth has accepted the recommendations of the May 1982 GAO report that he "Direct the Joint Subcommittee on Human Nutrition Research to develop a Federal nutrition research plan." This conference is subtitled "An Information Exchange Activity of the Joint Subcommittee" and is a necessary component of a coordinated and comprehensive research plan. However, I trust that following this conference the Joint Subcommittee and all of you here today will be ready to move beyond information exchange, definitions of nutrition research, identification of priority research activities, and research classification systems and data elements to the process of developing a comprehensive plan for action. During this process you can waste a lot of time, i.e., you can spend a lot of time working on the details that I have enumerated today, and forget that the larger goal is to develop a plan to guide resources and to use them in developing answers to problems.

Frankly, I was somewhat surprised to learn that these components of Federal nutrition research management and planning were not in place prior to the establishment of the Joint Subcommittee. I was also surprised to learn during my 1981 DORFA Subcommittee hearing on nutrition research that a management information system for human nutrition research did not exist at the Federal level or that the Executive Branch did not categorize nutrition research expenditures by Agency and area of support on a systematic basis. The lack of an on-line system and the fact that the data could not be compiled until nine months or more after the close of a fiscal year, prompted me to introduce the mandate for a "Plan for a Human Nutrition Research and Information Management System" in the Agriculture and Food Act of 1981.

I can assure you that this will be a continuing mandate, i.e., the same or stronger language will be in the Agriculture Act of 1985, the Act of 1989, and so on into perpetuity. I have been putting this kind of language, with successive refinement, into a wide range of legislation for many years. For example, I am sure you know that similar language pertaining to all of science exists in the Science Policy Act that mandates the Five Year Outlook for Science and Technology as a whole. Similar language also exists with regard to resource planning in the Forestry Act and many other Acts. This action results not only from my personal interest, although I have been involved in all of these aforementioned Acts, but from the growing awareness of many Members of Congress that only this kind of approach will allow the Congress to measure results, to make wise decisions about allocating resources, and so on.

I understand the development of the Plan for a Human Nutrition Research and Information Management System, not to mention the implementation, was not a simple task. Let me assure you that the process of developing a comprehensive human nutrition research plan will be even more difficult and frustrating. The planning process will not be successful or productive if controversies do not arise over the planning strategy itself; i.e., who will and should undertake this planning and its implementation, what are the future perspectives and trends, and how much planning is needed to direct change.

All of you know that planning is controversial and sometimes even polarizing, and I don't want to focus on that aspect of planning. I don't want this plan to become controversial and polarizing; the reason why this often results is due to the planning process itself. Some planning is antidemocratic, authoritarian, dictatorial, and counterproductive. I don't want to see that happen in any kind of planning that involves science. Other planning is participatory, it involves the best thinking of the user group, the client group, or all people who have something at stake. This kind of planning seeks to integrate their views into a purposeful program which aids the planning process. That is the kind of planning that we need to look at. It is not so much the concept, but the fact that people frequently do not distinguish between good democratic planning and bad authoritarian planning. This is what we need to be concerned with.

It would appear that before a comprehensive plan for Federal human nutrition research can be developed that two complex policy questions need to be articulated:

1. What should the Nation's human nutrition research goals be and what benefits to society can be realized by achieving these goals?

2. What role should the Federal government play, versus other sectors of society, in achieving these national human nutrition research goals?

These are both very fundamental policy questions you need to ask yourselves. They are generic. We are asking ourselves these questions not only about nutrition research; just yesterday we visited with the Director

of the National Science Foundation and we raised these same questions about science education, engineering research, and a whole host of other similar issues. We need to keep these questions before us at all times.

Unless national goals and the relative roles of the various sectors of society are defined, it will be difficult, if not impossible, to develop a meaningful plan for the Federal nutrition research module and select an effective planning mechanism. However, the planning mechanism you choose should provide a means to move beyond conflicts over assumptions, biases, and turfs to realistic choices through workable compromises. To be effective, the planning process must be viewed as an experimental process and unsuccessful trials as learning experiences just as they are in the research and development processes.

I am surprised sometimes that scientists cannot seem to understand that most of the institutional experimentation they conduct should be regarded as a scientific process, in the same way as the research they conduct in a particular physical field. In fact, Congressmen should recognize that most of what we do is a scientific experiment, but because we do not recognize this we make a lot of mistakes, or fail to learn from our mistakes. You are much too smart to do that. You are certainly more intelligent than Congressmen, and I urge you to keep that point in mind.

Our similar effort in the climate research program, which I was involved with beginning several years ago, started with innumerable difficulties in making the proper institutional arrangements to do what you are trying to do. You might learn from analyzing the mistakes that have been made in the climate program, and see if you can go through the learning curve more rapidly as a result of that experience.

In order to obtain understanding and support for the priorities and expected outcomes of the plan, the planning process must also accommodate broad participation and provide for open communication about goals and assumptions. I believe experience has slowly taught us that decentralized or logical unit planning can more readily incorporate future needs and opportunities. Thus, perhaps GAO was correct in calling for a Federal nutrition research plan before a National plan is formulated. Even the Federal component may have to be developed through the integration of logical unit subsets or through interlocking research modules.

Whatever the Federal planning strategy, I believe the academic and private sectors should be involved in the process. This component is important to delineate the priorities of these groups and identify those activities which they can prepare to undertake to achieve National goals. This process will also assist in gaining their support and understanding of the Federal plan and the priorities which are identified as the necessary and proper role of Federal nutrition research programs. From my optimistic viewpoint, the objective of this broad participatory planning would be to motivate university, industry, professional, and consumer coalitions to join with the Federal government in developing not only National nutrition research goals, but ultimately a National nutrition research plan. Such a plan might also serve to identify the roles of the various players, who is best suited to undertake the responsibilities, and the resources required to

achieve the specified outcomes and their contributions to societal goals. It is obvious that the ultimate role of nutrition research is to get human beings to act more rational in terms of dietary intake. If the public is not involved in that process of determining the rational goals, then you are going to have a very difficult time getting them to do anything about it. This point seems so clear that it does not have to be belabored. Many times the public will allow the experts to come up with something that is absolutely letter perfect, and they'll tell you that they are not interested because you have not consulted with them and they really don't care very much about your expertise. I know that they treat politicians that way.

Regardless of whether the plan focuses on Federal nutrition research or on a more comprehensive framework, the resulting plan will be of limited value if viewed as a statement of policy to be defended against all adversaries. The role of the plan is that of consensus building and of a communication tool to its designers and constituents expressing an affirmation of goals and principles. Adjustment of the plan as conditions and perceptions change is a part of the process and should not be perceived as inconsistency or lack of foresight. The planning process, in spite of its frustrations, can be as important as the resulting document.

A comprehensive research plan, regardless of the discipline involved, is not the sole answer to generating new knowledge and creating appropriate mechanisms for putting that knowledge to use for the benefit of society. However, such a plan is certain to influence and assist the scientific community in addressing national needs and identifying opportunities to improve the flow of ideas between the laboratory, the marketplace, and the consumer. Hopefully, such a plan would also assist the Congress and the Executive Branch to move from today's preoccupation with budgets and administration to the role of science in addressing the Nation's economic problems and enhancing the quality of life. If some of you ever thought that we support science for any other reasons, you should change that perception. We have a very pragmatic approach to the support of science--either it does good for people, or we do not support it.

The plan I envision is not intended to be a mechanism for controlling nutrition research or dictating specific research activities which should be pursued by the implementators. Rather, the plan should serve as a guide for directing and motivating research that would achieve comprehensive nutrition goals as defined by the leaders of the numerous disciplines which encompass the science and application of nutrition. The plan must be sufficiently flexible to tap the creativity of individuals, maintain the integrity of the scientific process, and encourage centers of excellence.

I realize that the development of a comprehensive plan is not a simple or easy task. I also realize that there are few, if any, models to draw upon from other disciplines. However, I believe that nutrition has a major role to play in identifying the causes and the solutions to many of today's and tomorrow's health, economic, and social problems.

I am convinced that the science of nutrition has the potential to demonstrate the benefits of focusing a major portion of health related research on behavior modification and disease prevention rather than on treatment, and to set examples of how other areas of science and technology can plan

to more effectively deliver the products and services they offer society. The need for the continuation of basic research in relationship to prevention goals is well understood. However, to effectively implement the current concepts of "wellness," increased emphasis must be placed on research at the interface between biomedical and behavioral methodologies. How can we expect to modify behavior if we do not know the basis for such addictions as overeating and smoking, or the effects of stress on health? Likewise, social science research can make significant contributions to health, e.g., finding effective ways to communicate nutrition research results in a manner that would truly influence lifestyles.

I hope that I have convinced you through my simplistic, optimistic, and frequently dogmatic view of planning and priority-setting, to accept the challenge to place nutrition in the forefront of scientific leadership. I look forward to the results of both the planning process and the planning document. I trust that the outcomes will be a valuable experience for you and that you will discover new ways to generate a concept of priorities through a systematic process. Your success will challenge other coalitions of scientists and Federal agencies to experiment with the models you discovered and thus improve the effectiveness of both science and science planning.

It is even conceivable that your planning demonstration may help this Administration and those that follow to better understand the contributions of the social and behavioral aspects of nutrition and the importance of integrating food science, nutrition, and health research. I also trust that your planning demonstration will help to emphasize the importance of the National Nutrition Monitoring System. Surveillance and monitoring, including epidemiological investigations, are basic and essential to insuring the safety and quality of the food supply, to assuring that the nutritional needs of the public are met, and to assuring that an appropriate data base exists for planning future research needs and guiding the expenditure of public funds for nutrition research, programs, and intervention. Current budgetary actions proposed by OMB for these types of programs in agencies such as CDC, FDA, and HNIS indicate that this educational process is badly needed.

Let me emphasize that I attach a great deal of importance to what you are doing. I am interested in the process, the framework, and the implications of what you are doing in terms of improving man's process of increasing his knowledge and making use of that knowledge. I will be watching the results very closely. I am a politician, and frequently a partisan politician, but my main concern with my role is whether it will make an effective long-term contribution to the welfare of this country. I hope that you too will take a similar attitude with regard to your work.

Thank you very much.

UNITED STATES DEPARTMENT OF AGRICULTURE

USDA Human Nutrition Research Overview

By

Donald Therriault, Ph.D.

USDA HUMAN NUTRITION RESEARCH

OVERVIEW

The U.S. Department of Agriculture is authorized by legislation to provide the leadership, oversight, and management necessary to ensure that the Nation is provided with adequate supplies of high-quality food and fiber. Consequently, the Department has a long history of human nutrition research which dates back to the 1890's, and the classical work conducted by W. O. Atwater. However, the first explicitly stated authority to conduct human nutrition research came in 1946. The Research and Marketing Act of 1946 directed the Secretary to:

> "Conduct and to stimulate Research into the laws and principles underlying the basic problems of agriculture in its broadest aspects, including but not limited to...Research into the problems of human nutrition and the nutritive value of agricultural commodities with particular reference to their content of vitamins, minerals, amino acids, and all other constituents that may be found necessary for the health of the consumer...".

Later the Food and Agriculture Act of 1977 firmly established the USDA as the lead agency in the Federal Government for the food and agricultural sciences, and directed that research concerning food and human nutrition be established as a separate and distinct mission of the Department. The Act states:

"(a) Congress hereby finds that there is increasing evidence of a relationship between diet and many of the leading causes of death in the United States; that improved nutrition is an integral component of preventive health care; that there is a serious need for research on the chronic effects of diet on degenerative diseases and related disorders; that nutrition and health considerations are important to the United States agricultural policy; that there is insufficient knowledge concerning precise human nutritional requirements, the interactions of various nutritional constituents of food, and differences in the nutrition requirements among different population groups such as infants, children, adolescents, elderly men and women, and pregnant women; and that there is a critical need for objective data concerning food safety, the potential of food enrichment and means to encourage better nutritional practices.

(b) It is hereby declared to be the policy of the United States that the Department of Agriculture conduct research in the fields of human nutrition and the nutritive value of foods and to conduct human nutrition education activities..."

The USDA human nutrition research is a cooperative effort of the Department and state agricultural experiment stations, 1890 land-grant institutions, Tuskegee Institute, and other Universities. The primary responsibility

within USDA for human nutrition research lies with the Agricultural Research Service. However a significant amount of human nutrition research is also carried out within the Human Nutrition Information Service and the Cooperative State Research Service. The Department employs both intramural and extramural research to carry out its missions. The extramural research makes use of a number of mechanisms including:

Competitive grants
Formula grants
Contracts
Cooperative agreements

The objective of the human nutrition research programs is to:

Develop the means to promote optimum human health and well-being through improved nutrition.

To achieve this objective the Department has developed a number of approaches. These are:

1. Define nutrient requirements for humans at all stages of the life cycle.

2. Determine the nutrient content of agricultural commodities and processed foods as eaten and establish the bioavailability of these nutrients.

3. Improve the nutritional status of humans and the well being of families by making available techniques to assess the effectiveness of nutrition programs.

4. Collect, develop and disseminate information that will improve professional and public understanding of the nutritional adequacy of diets and food supplies.

This research is carried out within the Human Nutrition Information Service and the Agricultural Research Service. The Human Nutrition Information Service directs its attention primarily at:

- improving professional and public understanding of the nutritional adequacy of diets and food supplies;

- developing new knowledge needed to improve the nutritional quality of diets; and

- collecting and disseminating technical and educational materials on food and human nutrition.

The Agricultural Research Service maintains five major human nutrition research centers around the country. These research centers focus on major

components of the overall program. Scientists at the centers study a broad range of nutritional problems and in the process develop innovative methodologies that benefit scientists in many other fields. Between them the centers have developed a well coordinated, multi-disciplinary approach to an area of intense public and scientific interest. The knowledge gained through these efforts continues to increase our understanding of the important role that nutrition plays in human health and well being.

USDA Western Human Nutrition Research Center

By

James M. Iacono, Ph.D.

USDA WESTERN HUMAN NUTRITION RESEARCH CENTER

In 1978 Congress directed the Department of Agriculture to conduct a feasibility study of the Nutrition Unit of the Letterman Army Institute of Research at the Presidio of San Francisco as a possible site for a new Human Nutrition Research Center of the USDA. The study was conducted and it was concluded that the facility at LAIR had the necessary equipment and expertise required to conduct a research program focused on improving and developing new methods to assess the nutritional status of individuals and population groups.

Subsequently, Congress mandated that the nutrition research program of DOD be transferred to the USDA, along with 19 positions, metabolic nutrition unit and associated facilities, laboratory space, office space, and $1.0 million in funding to initiate the new human nutrition research center at LAIR.

To carry out the mandate of Congress, the new Center was given the mission of developing new methodologies to assess nutritional status as well as factors leading to malnutrition and to study human nutritional requirements. In order to achieve this mission, a multi-faceted research program was planned and developed. The plan called for research targeted to four principal areas of inquiry: (1) development of reliable, efficient and inexpensive methods for defining nutritional status; (2) identification of the factors, forces and trends resulting in malnutrition; (3) studies of human nutritional requirements; and (4) development of nutritional criteria and methodologies to assist in the design and evaluation of nutrition action programs.

The planned program for the Western Human Nutrition Research Center (WHNRC) is only partially implemented. Considerable effort was expended during the first two years of operation to modify the existing space transferred to USDA by DOD into usable laboratories and a functioning metabolic unit. The core of expertise transferred from the DOD, although small, has served as a foundation for building the research program. An intial objective was to place the Human Nutrition Suite into operation and to recruit and train personnel necessary for its operation. This has been accomplished.

A major part of the mission of the WHNRC is to develop methodology to assist the Food and Nutrition Service (FNS) of USDA to assess the effectiveness of its programs. Programs of FNS are designed to strengthen the economy and to safeguard the health and the nutritional well-being of the nation. Of the various assistance programs administered by NFS there are three major categories which ARS nutrition research supports through methodology development. These are: (1) the Food Stamp Program; (2) the school feeding programs; (3) the Women-Infant-Children program.

In support of these programs, two areas where WHNRC will focus its immediate attention include: (1) the development of improved methodology for collection of dietary intake data; and (2) the development of better anthropometric indicies of nutritional status.

In regard to methodology development for the improvement of food consumption information, the collection of dietary intake data typically involves the use of some variant of the 24-hour dietary recall, diet history, or food frequency methodology. The ability to detect the effects of FNS food intervention programs on dietary intake is often obscured by extraneous sources of variants associated with measurement area, method of data collection, instability of the behavior being measured and specific characteristics of program participants (e.g., age and sex) which may interact with the nutritional methodology employed. For these reasons, the research on collection of data for dietary intake will be focused to identify the major sources of variation that distort estimates of food intake and arriving at empirical estimates of how much variation is due to each of these sources.

Once the sources of variation have been identified, a series of measures and protocols need to be developed which can be administered in large scale field studies which are cost effective, sensitive to modest program impacts, minimally obtrusive and will reduce extraneous sources of variation. Finally, the revised and approved measures will need to be field tested on a sample population representative of participants found in selected FNS programs.

The development of anthropometric indicies of nutritional status to assess the impact of the food assistance programs of FNS also represents an area of study high on the priority list of WHNRC. While advances have occurred in the development of dietary methodologies to assess nutritional impact, less attention has been directed at the development of sensitive anthropometric measures and indicies that can be used to assess modest changes in growth, physical development and body composition in infants and children. Of great interest is the use of nutritional status indicies to predict the state of obesity in individuals, that is, the degree of leanness or overweight, since obesity has been shown to be a significant nutritional problem in most FNS program participants. Validation of anthropometric measures by simpler methods, therefore, is desired. Alternatives to current anthropometric measures which can be administered reliably and cost effectively under field conditions are presently being sought by FNS.

It is important that in our approach toward methodology development, standardization of anthropometric methodologies and the establishment of appropriate norms for the analysis of body composition be developed.

Other areas for the development of methodology for nutritional status of individuals and population groups include the development of new biochemical, immunological and physiological techniques that may be applied in the conduct of field operations for nutrition intervention programs. Micro methods for constituents of blood and urine should be developed with the use of high performance chromotography to assess the nutritional status for nutrients such as vitamin A, vitamin B_6, iron and zinc. Development of functional tests will have to be considered whenever feasible. Serum, leukocyte, platelet, or erythrocyte enzymes associated with specific nutrients should be explored. Nutrients for study include vitamin B_6, pantothenic acid, niacin, zinc and iron. The use of functional measurements should be investigated for application in the assessment of various nutrients. Newer methodologies developed in the laboratory and with

animal models should be modified and applied to the human to better assess nutritional status.

Another classical approach used by the Center will be that of studying factors influencing the nutrient requirements of men and women at all stages of the life cycle. Objectives of these studies will be to identify and quantitate factors that may influence the nutrient requirements for individuals. Several studies have already been conducted in adult men and women volunteer subjects maintained under controlled dietary conditions on the Human Nutrition Suite of the Center.

Finally, the Center will be involved in the development of field nutrition evaluation methodology. The objective of this area will be to develop nutritional methodology and criteria for design and evaluation of nutritional intervention programs and will identify socio-economic factors, forces, and trends associated with the development of malnutrition. Information that is presently available from recent nutritional surveys and field studies and controlled human nutrition investigations needs to be analyzed for approaches to be used in the evaluation of intervention programs. There is a need to apply existing data bases obtained from field studies to socio-economic data that will identify potential factors that may result in malnutrition. At the same time, it is important to validate results of socio-economic factors with data collected from nutritional status monitoring tests.

USDA Beltsville Human Nutrition Research Center

By

Walter Mertz, M.D.

USDA BELTSVILLE HUMAN NUTRITION RESEARCH CENTER

BACKGROUND:

The history of the Beltsville Human Nutrition Research Center can be traced without interruption to 1894 when human nutrition investigations were authorized by the Congress to be conducted by the Office of Experiment Stations with Headquarters at Westland University, Middletown, Connecticut. In 1906 the Headquarters of human nutrition investigation were moved to Washington, DC, and in 1941 the laboratories of the Food and Nutrition Division moved to the Agricultural Research Center in Beltsville, Maryland. The human nutrition research activities continued at Beltsville in spite of numerous reorganizations and of changing names to the present.

MISSION:

The BHNRC has as its mission the more complete definition of human requirements for essential nutrients through basic and applied research, and the identification of foods that meet the nutritional requirements through nutrient composition research.

ORGANIZATION:

The Beltsville Human Nutrition Research Center employs approximately 100 persons, of those 43 are scientists. The research activities are organized in five laboratories addressing human nutrient requirements for the major nutrient groups (carbohydrates, lipids, proteins, energy, vitamins and minerals) and nutrient composition research. In addition, there is a modern human study facility that allows the simultaneous performance of two independent dietary studies. The annual budget of the Center is approximately $4,952,400. This budget, except for some collaborative agreements with local universities and medical schools is entirely spent for intramural research. The research activities will be discussed by individual laboratories.

1. Carbohydrate Nutrition Laboratory

Operational Objectives: To determine the effect of utilizable carbohydrates (e.g. sucrose, fructose, starch) and non-utilizable carbohydrate (dietary fiber) on the levels of metabolic risk factors associated with degenerative disease and nutrient bioavailability and to investigate the mechanisms responsible for the differential metabolic effects of dietary carbohydrate.

The Laboratory studies the effects of different levels of dietary sugars on glucose, lipid, and hormone metabolism with the aim of making quantitative and qualitative recommendations for a sugar intake that is compatible with a minimum influence on recognized risk factors for cardiovascular disease. For example, work in this Laboratory has led to the identification by simple biochemical measurements of "sucrose-sensitive" human subjects for whom even a moderate sucrose intake elevates serum lipids, serum insulin and results in

impaired glucose tolerance. The Laboratory also studies metabolic effects of fructose which is increasingly consumed by the U.S. population. Another major concern is the investigation of the effects of different types and amounts of dietary fiber on mineral availability and balance, with the aim of identifying types and amounts of dietary fiber that are beneficial to intestinal function but that do not adversely affect the biological availability of essential minerals and trace elements. Studies are also underway in experimental animals on the different efficiency of energy utilization as influenced by the nature of the major sugar component of the diet.

One principal accomplishment of the Laboratory is the demonstration that most human subjects do not react adversely to moderately high intakes of sucrose, but that an approximate 10% of the subjects studied predictably responds to even low sucrose intakes with a significant elevation of plasma lipids.

2. Lipid Nutrition Laboratory

Operational Objectives: To determine the effects of type and amount of dietary fat on blood lipids and lipoproteins, blood pressure, coagulation and other risk factors associated with cardiovascular disease, and to investigate mechanisms whereby essential fatty acid intake may change such factors.

These studies involve controlled long-term experiments with human volunteers, epidemiological studies in Europe and animal experiments measuring the effects of special diets on blood and tissue levels, platelet function and prostaglandin metabolism. A principal acccomplishment of this Laboratory, several times repeated and independently confirmed, was the observation that a moderate reduction of dietary fat content from 40 to 25% of the energy and an increase in the ratio of polyunsaturated to saturated fatty acids resulted in a significant reduction of elevated blood pressure in the subjects, a beneficial effect on clotting parameters and, as expected, a significant reduction of circulating lipids. Over the years, the Laboratory developed a large number of menus that provide the effective diet in a form that is acceptable to the average person in the United States and in Finland. The long-range goal of this research is the identification of the dietary level of saturated fats and of essential fatty acids that are responsible for the observed effects. Also, the elucidation of mechanism of action, for example via prostaglandin metabolism and/or membrane properties and interactions of dietary fats with other essential nutrients.

3. Protein-Energy Nutrition Laboratory

Operational Objectives: The determination of human energy requirements as modulated by dietary factors and energy expenditures, determine the interactions between proteins and energy and proteins and minerals and trace elements. Also, studies the nutritional qualities of fermented milk and measure their effect on performance in experimental animals.

This Laboratory was recently redirected toward the above objectives. Energy measurements are being performed in experimental animals and, in preliminary studies, in human subjects. The activities will accelerate when the direct human calorimeter, now on order, becomes operational. An example of progress in the protein-mineral interaction was a study on 62 free-living families on the effect of various soy products as partial substitutes for meat on nutritional iron status. The results, when fully evaluated will establish whether the observed impairment of iron absorption by soy products in acute experiments affects nutritional status.

4. Vitamin and Mineral Nutrition Laboratory

Operational Objectives: To determine requirements and mode of action for specific vitamins, minerals and trace elements. To identify chemical forms and biological availability of these micronutrients in foods consumed by humans. To develop sophisticated analytical instrumentation and techniques for assessment of trace elements and vitamins in human nutrition.

The Laboratory concentrates its efforts on the essential trace elements, iron, zinc, selenium and chromium and, among the vitamins, B_6, and vitamins A and E. A typical accomplishment is the recent demonstration in a double-blind, placebo controlled study of a significant improvement of impaired glucose tolerance during supplementation with physiological amounts of chromium. The Laboratory has established outstanding analytical facilities in clean-room facilities and collaborates with researchers in the United States and abroad. In the vitamin area the Laboratory demonstrated that breast milk of mothers provided substantially less than the Recommended Dietary Allowances for vitamin B_6 to the infant, even when the mothers were supplemented with vitamin B_6. The Laboratory continues to be involved in several international coordinated studies on trace elements.

5. Nutrient Composition Laboratory

Operational Objectives: To provide essential data on the nutrient content of foods as consumed in the United States.

These objectives are accomplished by (1) analyzing the nutrient content of foods with tested, dependable assay techniques and supplying the results of these analyses to appropriate groups and agencies, (2) designing and developing either new or improved methodologies for the analysis of nutrients in foods by conducting appropriate research in chemistry, biochemistry and biology, (3) developing and utilizing sound sampling techniques for the U.S. food supply to insure that representative samples are analyzed for their nutrient content, (4) planning, developing and conducting appropriate research on the effect of food processing procedures, transportation and marketing methods, as well as home, institutional and restaurant food preparation procedures, on the nutrient content of foods. The Laboratory has recently moved into a completely remodeled building that meets all the requirements of modern food analysis. The Laboratory has a well established group on lipid analysis in foods which is

collaborating with the National Heart, Lung and Blood Institute; in the mineral and trace element field it has perfected a multi-element analytical method for trace elements in foods; a carbohydrate group is establishing reliable methods for measurements of sugars and various types of fiber in foods and the vitamin group has developed validated methods for vitamin B_6 and is doing methodology research for vitamin C, thiamine, and folacin, carotenes and vitamin A. Results of the routine analyses of the Laboratory are submitted for inclusion in Agriculture Handbook 8 and are published in the scientific literature.

USDA Human Nutrition Research Center on Aging
at
Tufts University

By

Hamish N. Munro, M.D.

USDA HUMAN NUTRITION RESEARCH CENTER ON AGING AT TUFTS UNIVERSITY

The mission of the HNRC is to examine the relationship of nutrition to the aging process throughout adult life and the determination of dietary needs of people who are already elderly. Scientists at the HNRC are addressing three general questions of central importance to this mission: 1) How does nutrition influence the progressive loss of tissue function with aging? 2) What is the role of nutrition in the genesis of major chronic degenerative conditions associated with the aging process such as osteoporosis? 3) What are the nutrient requirements necessary to maintain the optimal functional well-being of older people? HNRC research projects are classified into major program areas including nutritional epidemiology, functional systems, nutrient requirements, nutrient metabolism, and drug-nutrient interactions.

1. Program in Nutritional Epidemiology and Nutrient Needs

This program encompasses a survey of free-living elderly in the Boston area, a special study for detection of vitamin K deficiency, and an epidemiological study of nutrient status and eye diseases.

A. Nutritional Status Survey: The primary objectives are: 1) To describe the distributions of nutrient intakes and of their blood levels in selected free-living and institutionalized elderly populations of men and women over age 60. 2) To compare nutritional status in free-living and institutionalized subjects. 3) To determine medication and vitamin-mineral supplement usage patterns in elderly populations and study drug-nutrient interactions. 4) The identification of elderly subjects by nutritional level for further HNRC studies.

To date, approximately 850 volunteer subjects have been assessed completely. This includes about 200 Chinese subjects as part of a separate survey at the Boston South Cove community. Preliminary results have indicated an appreciable prevalence (5-12%) of low blood nutrient levels for the B vitamins, and fat-soluble vitamins E and K, while only 3% of low values were found for indicators of vitamin C, vitamin A, protein, and mineral status.

B. Specific Test for Vitamin K Deficiency: A new procedure for detecting inadequate intakes of vitamin K has been developed. Current studies determining the nature and prevalence of subclinical vitamin K deficiency in the elderly may lead to clues relating this condition to common disorders of old age. In the absence of vitamin K, vitamin K-dependent carboxylase activity is inhibited and an abnormal form of prothrombin (lacking gamma-carboxyglutamic acid and measurable by radioimmunoassay) circulates in human plasma. This abnormal form of prothrombin has no coagulant activity and impaired metal binding properties.

C. Epidemiology of Eye Diseases in Elderly with Emphasis on Nutrient Status: Degenerative visual dysfunction in the elderly is common although few etiologic factors, especially in nutrition, have been identified. This project is undertaking three distinct case-control epidemiologic investigations

exploring the potential association between nutrient status and surgically defined cataracts, neuro-retinal and higher visual disorders, and senile macular degeneration.

2. Program in Functional Systems:

The objective in this program is to develop techniques for studying organ and tissue function during aging and to relate these changes to nutritional status. Thus the effect of nutrient status on animal tissue function and on human function are being pursued. The human measurements of tissue change with aging will also provide functional tests to apply to the free-living elderly population studies on nutritional status.

A. Gastro-Intestinal System:

(1) Regulation of Active Intestinal Electrolyte Transport in Aging: The goal of this project is to further understanding of the effect of aging on active intestinal transport in the context of calcium regulation of basal absorption and stimulated secretion and the biochemical mediators of these effects.

(2) Hepatic and Gastrointestinal Function in Aging as Related to Nutrition: Several disorders occurring in the elderly appear to be related to chronic malabsorption of vitamins and minerals or to an altered enterohepatic circulation of bile acids and fat soluble metabolites. The goals of this project are to measure hepatic, enterohepatic, and intestinal function in an elderly population and compare the data with those obtained in young healthy adults.

(3) The Effect of Gastric Atrophy in the Elderly on Folic Acid and Vitamin A Absorption: Folic acid and certain fat soluble vitamins are known to be commonly deficient among the elderly. A high intraluminal pH in the proximal small intestine is known to inhibit absorption of folate and fat soluble vitamins. Gastric atrophy is present in 30% of people over the age of 60 and results in an elevated proximal small intestinal pH. This study examines the effect of gastric atrophy on folate absorption and on vitamin A absorption.

B. Skin:

(1) Nutritional and Age Associated Changes in Cells Derived from Skin: Skin presents an obvious example of the aging process yet little is known of the basis for the dermatological changes observed. This project will utilize serum-free systems for the cultivation of human keratinocytes, melanocytes, endothelial cells and fibroblasts to examine age associated alterations in ultraviolet radiation.

C. Vision:

(1) Nutrition and Cataract Formation in Humans and Animals: Animal studies have provided direct evidence suggesting that malnutrition contributes directly to cataract formation. Weanling rats are fed diets rich in

galactose, glycine, or hydroxyproline and lens removed and analyzed for disturbances in oxalate metabolism. A clinical component of this study will consist of cataract patients over 60 years old and a matched control group.

(2) Vitamin A Absorption and End Organ Utilization: This project is concerned with the assessment of vitamin A nutriture and the effects of age and disease on vitamin A metabolism. The study involves the development of a rapid noninvasive visual test to functionally screen for vitamin A deficiency. Assessment of the effect of protein deficiency on vitamin A metabolism and utilization in human subjects and animals is being undertaken.

(3) Mechanistic, Regulatory and Physiological Roles of Eye Lens Proteases: Aberrant proteolysis is related to the development of eye-lens senile cataract. The dry weight of the lens is all protein and there are many lenticular proteases, yet in most eye lens there is only very limited proteolysis. Comparison of proteases and elucidation of proteolytic regulatory phenomena in the aging human lens and in rapidly metabolizing tissue will shed light on the causes of cataract and on the regulation of protein turnover.

C. Musculo-Skeletal System:

(1) Calcium-ATPase in Bovine Parathyroid Cells: The physiology of the parathyroid hormone is closely related to the physiology of calcium and phosphate metabolism, the function of vitamin D, and the formation of bone and teeth. The cytosolic calcium concentration appears to be important in regulating parathyroid hormone release. Calcium-ATPase may function as a calcium extrusion pump which regulates cytosolic calcium concentration. Kinetics and localization within the cell of the enzymes are being characterized.

(2) Effect of Vegetarian Diets on Osteoporosis: Estrogens and vitamin D play a major role in the formation and maintenance of normal bone structure. The clinical component of this project is designed to investigate the effects of an omnivore versus a vegetarian diet on serum hormone levels (estrogens, vitamin D_3, 25-hydroxy-, 1,25-hydroxy-, and 24,25-dihydroxy-vitamin D, parathyroid hormone, calcitonin, calcium and phosphorus) and bone density of the wrist and aleveolar ridge (via photon absorptometry) and spine (via CT scan).

(3) Comparison of Treatment Regimens for Osteoporosis: The etiology of hepatic osteodystrophy appears to be multifactorial, involving such factors as malabsorption of calcium and phosphate, alterations in vitamin D metabolism, treatment with cholestyramine, poor nutrition, and perhaps other unrecognized abnormalities of bone metabolism related to prolonged cholestasis. The osteoporosis of primary biliary cirrhosis is an illness that resembles postmenopausal osteoporsis histologically although bone changes occur more rapidly allowing for prospective studies on measurement and treatment modalities. This study will evaluate treatment of biliary cirrhotic patients with calcium and vitamin D with or without the addition of sodium flouride.

3. Program in Nutrient Metabolism:

A. Protein and Energy Metabolism in the Elderly: Studies are being made on the protein metabolism of old versus young subjects in order to determine the role of dietary protein and energy intakes in the preservation of active body tissue. First, a comparison has been made between old and young adults in order to determine an adequate amount of protein to maintain nitrogen balance. Second, attention has focussed on the long-term loss of body protein, measured by ^{40}K. Much of this loss has been attributed to muscle. Third, we have used amino acids labeled with stable isotopes to follow plasma protein metabolism in elderly human subjects. Finally, we have devised a new technique for measuring synthesis of plasma glycoproteins by labeling intact animals with 1-H^3-galactose and measuring the specific activity of the free linear galactose pool of the liver by causing excretion of its equilibrium product glucuranic acid by administering drugs excreted in the urine as glucoromides. We hope to adapt this procedure to man in order to show the effect of aging on plasma glycoprotein in such conditions as acute phase protein induction, etc.

B. Diet, Amino Acid Metabolism, and Exercise in Adult Humans: This study is designed to investigate the effects of exercise training on functional capacity, skeletal muscle metabolism, and whole body protein turnover in elderly and young healthy humans. The practical purpose of this study is to determine to what extent a controlled physical training program can improve functional capacity in the elderly. Another objective is to find out how training-induced metabolic and compositional changes in muscle are interrelated with whole body protein metabolism, both at rest and during exercise.

C. Lipoproteins, Nutrition, and Aging: The Lipid Metabolism Laboratory has been established at the HNRC to examine the interrelationships among lipoproteins, aging, and nutrition. Its objectives are to examine the following areas: 1) Identification of nutritional and other factors associated with age related lipoprotein changes in the U.S. population (increased LDL levels). 2) Characterization of the lipoprotein profiles, lipoprotein metabolism, genetics and nutritional status of octagenarians with no clinical evidence of coronary artery or cerebrovascular disease (especially kindreds with decreased LDL or increased HDL plasma concentrations). 3) The relationship between alterations in nutritional intake to changes in plasma lipoproteins, and determinants of enchanced dietary responsiveness such as alterations in apolipoprotein isoforms, apolipoprotein carbohydrate content or composition, decreased HDL, abnormal LDL, changes in hormonal balance, and the aging process.

D. Protein Metabolism in Arterial Smooth Muscle Cells: The goal of this research is to study the origin of cells found in cardiovascular degenerative conditions associated with aging and nutrition. The approach utilizing smooth muscle cells in tissue culture will provide new insight into the mechanism by which nutritional conditions influence the development of vascular disease.

E. Nutrition and Cell Programming in Relation to Aging: One aspect of aging with potential for modification by nutritional status is the programming

of cells to function throughout life. This research direction within the Program in Nutrient Metabolism is aimed at studying the effects of long-term dietary conditions on various aspects of cell control mechanisms that are sensitive to age-related changes.

4. Program in Drug-Nutrient Interactions:

A. Role of Vitamin E and Selenium on Lipid Peroxidation with Age: Lipid peroxidation, particularly of polyunsaturated fatty acids can lead to changes in the physical state of membrane lipids and associated functions of transport permeability and receptor activity, and to accumulation of ceroid and lipofuscin age pigments. The purpose of this study is to investigate the free radical hypothesis of aging and the antioxidative role of vitamin E and selenium in tissues of weanling and senescent rats fed deficient diets and determine the relative susceptibility to oxidant-induced injury and the degree to which such risks are age dependent and tissue specific.

B. Effects of Steroid Hormones on Human Protein Metabolism: Synthetic glucocorticords are widely used in the elderly for treating arthritis and other age-related conditions. The influence of dexamethasone on protein metabolism and the metabolic fate of leucine within the skeletal muscle will be examined via the use of stable isotopes of leucine, alanine and urea. In addition, earlier studies using anabolic steroids (methandrostenolone), which have been largely restricted to young athletes, will be refined and repeated in elderly subjects to determine induced changes in whole body protein muscle metabolism.

C. Effect of Age, Body Habitus, and Nutritional Status on Drug Kinetics and Dynamics: Drug disposition is substantially influenced by the physiochemical characteristics of the drug and the body habitus of the exposed individual. This project will evaluate the effect of changes in body composition associated with aging, such as the increased proportion of body fat to lean body mass, on drug disposition and clearance as well as on clinical drug effects as evaluated by well-validated tests of intellectual function and psychomotor performance. In addition, the effects of acute and chronic changes in diet on these parameters will also be evaluated. Selection of drugs to be tested is based upon clinical and pharmacokinetic factors. Additional studies focusing on sedative/hypnotic agents will provide objective data on sleep and insomnia in the elderly, their relation to body habitus and nutritional habits and the effect of drug use and discontinuation.

D. Prostatic Enlargement in Relation to Vitamin A Status: The purpose of this study is to examine morphological events which accompany the development of experimentally induced prostatic hyperplasia in young and aged mice and its reversal by beta-retinoic acid. Ventral prostate explants are being fixed for light and electron microscopy and analyzed via standard morphometric techniques as well as colcemic metaphase arrest and ruthenium red analysis. These experiments will help elucidate the cellular mechanisms involved in prostatic hyperplasia and how these processes are influenced by aging, hormones, and retinoids.

USDA Children's Nutrition Research Center
at
Baylor College of Medicine

By

Buford L. Nichols, M.D.

USDA CHILDREN'S NUTRITION RESEARCH CENTER AT BAYLOR COLLEGE OF MEDICINE

INTRODUCTION:

The measurement of nutritional needs and the attainment of optimal nutritional status in the pregnant and lactating woman and in the child from conception to adolescence is the foremost mission of the Children's Nutrition Research Center (CNRC). To reach this objective, emphasis has been given to the development of precise methods for the investigation of normal nutrient needs, for the determination of the relationships between nutrition and normal growth and development, and for the definition of biochemical and physiological standards for normal growth and nutritional status.

The CNRC has completed four years of service under a Cooperative Agreement between the United States Department of Agriculture and Baylor College of Medicine. Twenty-four scientists are employed at the CNRC, which is housed in a leased facility that consists presently of 16,935 square feet and is ideally located adjacent to the Texas Children's Hospital. In addition, the Stable Isotope and Lactation Programs receive additional support from NIH. There are clinical research facilities for infants and children at the Texas Children's Hospital, the Ben Taub General Hospital, and the Jefferson Davis Hospital, all located in Houston. A large "Human Milk Bank" provides resources for the study of pregnant and lactating women and access to supplies of human milk sufficient for research purposes. The resources of the health care system affiliated with Baylor College of Medicine allow full access to a normal subject population for all of the research programs in the CNRC.

1. Lactation Program:

The mission of this program is the study of nutritional needs during human lactation. Based on the premise that human milk is the standard for infant feeding, investigations are focused on evaluations of the functional benefits of human milk. Studies are conducted which describe the composition of human milk through all stages of lactation, assess the functional significance of specific human milk components, and estimate maternal nutrient needs during lactation.

As lactation progresses, the concentrations of human milk constituents undergo changes, seemingly in response to changing needs of the maturing infant. During the past year, studies have been conducted to assess the changes in milk composition through twelve months of lacatation. Women were studied who were weaning their infants or who were continuing with unrestricted lactation after other foods had been added to the infant's diet. A number of nutrients and immunological components were measured, e.g., studies of secretory IgA antibodies specific to a pool of *E. coli* somatic antigens were of particular interest. Evidence was obtained to support the view that a functioning entero-mammary pathway continues through the first year of lactation. This pathway was found to persist even during weaning when the infant's intake of human milk was restricted. Evidence also was obtained that strongly suggests that a significant degree of compartmentation of immunological components and possibly of some

nutrients is found within the complex mixture of human milk. Immunological techniques have been used to detect increasing quantities of specific proteins after various degrees of digestion of human milk. Digestion was effected by centrifugation or heating with short-time, high-temperature techniques. The physiological development necessary for infants to utilize compartmentalized components fully is a question which is undergoing continuing investigation.

The normal daily intakes of exclusively breast-fed infants one- to four-months-of-age also have been estimated. Partial analysis of the data indicate much lower intakes than predicted based on prior estimates of the nutrient requirements of this age group. Women planning to breast-feed their infants were recruited prenatally and followed for four months. Twenty-four-hour milk intakes were measured and from these data and analyses of 24-hour milk aliquots, the amounts of energy, protein, fat, lactose, sodium, potassium, iron, zinc, calcium, phosphorus, magnesium, secretory IgA, lactoferrin, lysozyme, and SIgA antibodies specified to a pool of E. coli somatic antigens consumed by infants in a 24-hour period are being estimated. Partial analyses of data from 19 infants suggest intakes of energy (kcal/kg/day) of 109, 81, 69, and 72 at month 1, 2, 3, and 4, respectively. Analogous intake levels for protein (g/kg/day) are approximately 1.6, 1.3, 1.2, and 1.2. Relationships between growth and intake are being assessed. Growth in these infants remained within normal limits but rate of gain tended to be slower than that predicted by NCHS standards. These data question the appropriateness of growth curves derived from studies of infants fed synthetic formulas.

Studies that assess the efficiency of nutrient utilization in infants fed human or artificial milks are underway. These studies focus on the adaptations infants must make to either high or low levels of nutrient intakes. The Lactation Program, in collaboration with the Stable Isotope Program, is evaluating methodologies for the measurement of total body protein turnover and amino acid utilization in infants at high or low planes of nutrition. Other approaches also are being evaluated to investigate the rate and pattern of oxidation of amino acids, fat, and glucose in children after a meal at high or low planes of nutrition. Studies have collected data on maternal diets and changes in maternal body composition during the period of lactation. Relationships between these variables, the amount of milk produced, and its composition are being examined.

Numerous components with biological activity have been found in human milk. These constituents have been characterized as inductive, carrier, immuno-protective, and digestive agents that contribute functional benefits prior to their digestion and subsequent actions associated more commonly with nutrients. The full significance of these components, and of the changes which occur in their concentrations during lactation, is not understood; however, a consensus is emerging that broadens our concept of nutrients to include these complex organic constituents. The significance of these constituents to the nutritional well-being of infants is being investigated in clinical feeding trials of newborn premature infants. This work is being done with partial support from the National Institute of Child Health and Human Development. Infants are fed at equal protein and caloric levels either milk from their own mothers that has been fortified with human milk constituents or totally synthetic formulas. Growth,

composition of weight gain, clincial tolerance, and the maturation of gastrointestinal, renal, and immunologic functions of these infants are being assessed. Initial results suggest differences in the bioavailabilities of fats and minerals and in the retention of selected minerals.

2. Weaning Program:

The mission of the Weaning Program is to determine foods that should be introduced into the infant's diet to supplement maternal milk and to investigate the disorders of the gastrointestinal tract that occur as a consequence of inappropriate weaning.

An epidemiological investigation of carbohydrate intolerance in small infants has been completed this year. One of the major findings of the study was that infants who developed malnutrition with acquired monosaccharide intolerance (AMI) had lived in crowded environments and were born to younger mothers having had less favorable gestational histories than those infants who developed only acute gastroenteritis. Transient malabsorption of simple sugars in the small bowel is not uncommon among young infants with acute gastroenteritis; however, the presence of persistent acidic pH in the stool together with loss of glucose into the stool is associated with chronic feeding problems and severe malnutrition. Nevertheless, not all equally malnourished infants develop AMI.

Studies of the utilization of dietary cereals by normal one-month-old infants have been carried out in conjunction with the Stable Isotope Program and indicate that the colon plays a major role. Utilization of dietary cereals was shown to be of equal magnitude to that of mono- and disaccharides and glucose polymers. Using the small differences in ^{13}C content between carbohydrates derived from corn as opposed to other botanical sources, the direct use could be demonstrated by appearance of the increased $^{13}CO_2$ in the breath of infants following a single feeding of carbohydrates from corn. Analysis of fecal ^{13}C content showed that less than 5% of the complex carbohydrates could have escaped absorption by the small intestine and colon. This study also demonstrated the feasibility of exploiting differences in the natural abundances of ^{13}C in nutrients derived from the two photosynthetic food chains underlying the bulk of all nutrients consumed by man. In a parallel study, results indicated that normal breast-fed infants digested a large proportion of the milk sugar in their diet in the colon.

A method for the recovery of a graded series of polyethylene glycols, MW 283-590, from urine after oral administration has been developed and validated for quantitative recovery. This polymer series is used as a probe of small intestine permeability to passively absorbed, non-metabolized molecules. Comparison of the size distribution of the recovered polymer series with the administered distribution may be expected to change as the consequence of intestinal disease or injury. Application of this method to patients with AMI is expected to provide a longitudinal measure of the progress and regression of intestinal disease changes in mucosal absorptive functions.

3. Stable Isotope Program:

The function of the Stable Isotope Program is to provide quantitative measures of nutrient bioavailability, absorption (or malabsorption), transport, utilization, and excretion in populations studied by the Weaning and Lactation Laboratories. These include the lactating mother, the pre-term and term infant, the child undergoing weaning, and the child whose clinical status compromises his or her nutritional status. The development of these quantitative measures involves the generation of nutrients labeled with the stable, non-radioactive isotopes of hydrogen, carbon, nitrogen or oxygen; the availability of instruments of the appropriate sensitivity, precision, and capacity to analyze samples collected fromthe study subjects; and the creation and validation of analytical methods that will permit quantitation of the nutrient or its derivative as well as its content of stable tracer.

A. Nutrients Labeled with Stable Isotopes: Many nutrients with specific labels of ^{13}C or ^{15}N can be obtained from commercial suppliers. During the past year, a variety of amino acids labeled with ^{13}C have been acquired, assayed, and prepared by the pharmacy for administration. A series of metabolites useful in studies of colonic metabolism, including uniformly ^{13}C-labeled starch, glucose, and specifically labeled volatile fatty acids have been added to the inventory, and nutrients whose ^{13}C concentration has natural divisions into high and low forms are being collected. Thus, glucose from potato starch and from corn starch have distinctly different concentrations of ^{13}C, and exchanging these nutrients in the formula or diet will produce corresponding changes in the respiratory $^{13}CO_2$ abundance. Such exchanges can be used to demonstrate directly the absorption and utilization of these nutrients as well as to determine the proportion malabsorbed, if present. Casein from cows on a "low" ^{13}C diet has been obtained in sufficient quantities to prepare infant feeding formulas, and efforts are underway to obtain casein from "high" ^{13}C cows. This will require supplementation of the forage with corn silage, sorghum, or millet and subsequent processing of the whole milk to obtain the casein fraction. Fermentative preparation of lysine labeled with two atoms of ^{15}N by feeding the microorganism with $(^{15}NH_4)_2\ SO_4$ has produced several batches of the free amino acid that have been purified for oral and intravenous administration. This product, which as more than 97% enrichment of ^{15}N in both amino groups, will be used in studies of protein synthesis and breakdown.

B. Methodological Developments: Competence in the recovery of nutrients and metabolites from plasma and urine has been increased with the establishment of methods for the recovery, purification, derivatization and analysis of leucine, lysine, bile acids, and pyridoximer forms by gas chromatography-mass spectrometry. Kinetic studies of plasma amino acids are now possible with one or more labeled amino acids, and measurement of the concentration of pyridoxine, pyridoxal and pyridoxamine, as well as the phosphorylated forms, and pyridoxic acid has been carried out by inverse isotope dilution. In this procedure, a labeled form of the pyridoximer is added to the sample prior to isolation, and after purification, measurement of the isotope ratio of unlabeled to labeled form will establish the original concentration of the vitamer, regardless of the losses incurred in purification. This method is

expected to provide new, and more reliable, values for B_6 vitamers in tissue, plasma, and urine.

C. Clinical Studies: Studies of the hydrolysis, absorption, and oxidation of lactose by term infants have been completed, together wtih a comparison with the utilization of glucose in the same infants. These studies, partially supported by NIH, employ ^{13}C lactose and ^{13}C glucose. They demonstrated that lactose utilization by term infants is complete: less than 19% of the calories associated with lactose were excreted in the stool, as determined by fecal ^{13}C measurements.

Studies of body composition in preterm, term, and young infants in which the total body water was estimated using $H_2{}^{18}O$ have been carried out with partial support provided by NIH. In these studies, conducted before the development of breath water vapor sampling technique, the use of urine samples before and after the administration of labeled water was compared with the use of plasma samples. In all cases, the fluid samples are equilibrated with 15% CO_2 in N_2 in a shaker bath for 72 h, during which time the ^{18}O of the water exchanges with the oxygen of the CO_2. ^{18}O content then is determined as the proportion of $^{12}C\ ^{16}O\ ^{18}O$ to $^{12}C\ ^{16}O\ ^{16}O$. When urine values were compared with plasma samples obtained 2, 4, and 6 h after isotope administration, total body water estimates from isotope dilution in urine were within 1% of the plasma value within 4 h. Earlier urine samples tended to underestimate total body water because of admixture of post-dose urine with urine secreted at an earlier time but not voided. Extension of these studies using only urine samples of premature infants on formula and fortified breast milk are now underway at Texas Children's Hospital.

Many of the functional measurements derived from the administration of ^{13}C-labeled substrates involve the ultimate oxidation of the carbon to CO_2. Before this labeled CO_2 appears in breath, it undergoes mixing with, and dilution by, the body's pool of bicarbonate. In order to calculate the percent of the dose recovered as $^{13}CO_2$, it is necessary to know (or measure) the recovery of labeled bicarbonate from an individual in whom the test is to be conducted. An alternative practice is to assume a constant recovery and apply this factor to all subjects. A comparison of intra- vs interindividual variation in bicarbonate kinetics following an intravenous bolus of $NaH^{13}CO_3$ revealed that in resting, fasted adults, a substantial proportion (40-50%) of the administered dose remains unexcreted even 6 h after administration. Thus, the practice of using a factor of 80% recovery, as is commonly done, results in an overestimation of recovery and an underestimation of true oxidation rate. The intraindividual variations were as large as the interindividual variations, which argues for the use of a population value. A detailed kinetic analysis of bicarbonate pools and fluxes has been carried out for fasted/fed, high protein/low protein, and resting/exercised subjects. These data are being tabulated and analyzed and are expected to provide a sound data base for future studies in adults; similar data will be obtained for infants and children, starting with subjects in acidosis resulting from diarrhea.

USDA Grand Forks Human Nutrition Research Center

By

Harold Sandstead, M.D.

USDA GRAND FORKS HUMAN NUTRITION RESEARCH CENTER

HISTORY:

Impetus for establishment of the Grand Forks Human Nutrition Research Center came from a 1963 report that evaluated Agricultural Research Service research in human nutrition and outlined needs for the future. This report was submitted to the Senate by Senator Milton Young of North Dakota and was subsequently published in the Congressional Record. The report pointed out the need for four regional clinical research units for studies of human nutrient requirements and suggested that the units be located in proximity to medical schools. Grand Forks Human Nutrition Research Center was the first of those laboratories. It is located adjacent to the Campus of the University of North Dakota, about two blocks from the Medical School.

ADMINISTRATIVE RELATIONSHIPS:

When established in 1970, the laboratory was a field station of the Human Nutrition Research Division of the Agricultural Research Service. With reorganization of the Agricultural Research Service in 1972, the Laboratory became the Human Nutrition Research Laboratory of the North Central Region. Subsequently, with the establishment of Human Nutrition as a separate administrative entity in the Science and Education Administration of the Department of Agriculture, the Center was transferred from the Agricultural Research Service to that program. Subsequently, the Laboratory was designated a Center. Human Nutrition was returned to the Agricultural Research Service in 1980. The Center is now one of four regional Centers for nutrition research in ARS and reports administratively to the North Central Regional Administrative Office in Peoria, Illinois.

STAFF:

The staff of the Center numbers approximately 125 persons; of these, 28 are federal employees and the remainder are cooperative state employees. The scientific effort at the Center is equivalent to about 12 SYs. The staff is interdisciplinary and has expertise in medicine, biochemistry, anatomy, pathology, immunology, analytical chemistry, physics, psychology, exercise physiology, dietetics, nursing and statistics. Graduate students and postdoctoral research fellows participate in the activities of the Center through a cooperative agreement with the University of North Dakota.

FACILITIES:

Total space of the Center is approximately 60,000 square feet. As originally constructed, the Center had about 20,000 square feet. This year, 20,000 square feet were completed to provide animal care facilities previously not available at the Center. Next year, an additional 20,000 square feet will be completed to provide a 14 bed clinical unit and supporting laboratories. At present, the Center has an 8 bed clinical unit. This space will be renovated into

laboratories and an outpatient dining area. Support equipment for clinical research at the Center include a whole body counter, an underwater weighing tank, exercise physiology equipment, a mass spectrometer, a plasma emission spectrophotometer and 2 atomic absorption spectrophotometers, various other spectrophotometers, an amino acid analyzer, a gas chromatograph, a liquid chromatograph, liquid scintillation and gamma scintillation counters. Laboratories for studies using animal models are comparably equipped. Data acquisition and analysis resources include a 1000 K memory computer and two smaller 64 K computers.

BUDGET:

The current budget at the location is approximately $3,121,500. About 38% is used for administrative and facilities support, 35% supports human studies and 27% supports research on animals and other model systems.

RESEARCH:

The research program at the Center is interdisciplinary. It is divided between studies that utilize animals and studies that utilize humans. Research is also conducted at other institutions through memoranda of understandings and cooperative agreements.

A. Research on animals investigates zinc, its role in metabolism, immunity, brain maturation, and behavior; copper, its role in lipid metabolism, cardiovascular function, and brain function; nickel, its role in metabolism, interactions with other trace elements, and deficiency; vanadium, its role in metabolism, and deficiency; arsenic, its role in metabolism, and deficiency; boron, its role in metabolism, and deficiency; iron, its role in immunity, and brain function; binding ligands affecting absorption and metabolism of trace elements; toxic elements and their interactions with essential trace elements; and histopathology trace element deficiencies.

B. Research on human volunteers emphasizes nutrient-nutrient and nutrient-non-nutrient interactions that affect bioavailability, metabolism, and requirements of macro and trace elements; metabolic and functional effects of mild deficiencies of trace elements; interactions of trace elements with vitamins and other nutrients that influence their metabolism; effects of exercise on nutrient requirements and metabolism; and the role of nutrients in neuropsychological function.

PUBLICATIONS:

Since 1971, the staff has published 144 technical reports, 82 reviews and symposium articles, 6 book chapters, 13 letters and editorials and 5 nontechnical and educational publications.

RESEARCH EXAMPLES:

A. Zinc deficiency during the critical period for brain development retards growth of the brain, in part, through suppressed synthesis of DNA and protein. Impaired maturation is exemplified by fewer and retarded migration of cerebellur granular cells, and grossly abnormal dendritic arborization of purkinje, stellate and basket cells. Behavior of nutritionally rehabilitated offspring subsequent to late intrauterine or postnatal zinc deficiency is abnormal. Among recent findings are impairment of long and short term memory by postnatal zinc deprivation (birth to weaning) and increased whole brain and hippocampal norepinephrine in zinc deprived weanling rats. Limited observations on Rhesus monkeys deprived on zinc during most of the third trimester of fetal life provide evidence that primate infants will also suffer brain injury if deprived of zinc during the critical period of brain development.

B. Nickel, arsenic and boron are essential for experimental animals. Nickel deprivation retards growth and results in increased death in newborn rats. Intestinal absorption of ferric iron is depressed. Arsenic deficiency impairs growth of chicks and results in increased serum uric acid in arginine fed animals. Boron deficiency impairs growth of chickens. Effects are most striking in vitamin D deprived animals.

C. Copper deficiency in rats results in myocardial injury with hypertrophy, infarctions, fibrosis, endocardial tumors, arrythmias, and sudden death. Serum cholesterol, uric acid and hemoglobin A1C are increased. The findings may be relevant to human health because many conventional human diets contain less than 1.0 mg Cu daily. Multivarient analysis of 131 balance studies indicate that the human dietary requirement for copper is 1.5-2.0 mg daily depending on the levels of zinc and protein present in the diet. The copper requirement also appears to increase when dietary fiber is increased. When a volunteer was fed a diet prepared from conventional foods that provided 0.7 mg Cu daily, for 16 weeks, the copper balance became negative, serum copper and erythrocyte superoxide dysmutase decreased, and serum cholesterol increased. Copper supplementation reversed these findings. When other volunteers were deprived of copper, intravenous glucose tolerance was impaired and apparent sensitivity to insulin decreased. Copper supplementation corrected these abnormalities. Copper deprivation was not associated with a decrease in sweat copper.

D. Metabolic evidence of zinc deficiency occurs irregularly in men fed conventional diets containing 3.0-3.5 mg zinc daily. In addition to negative zinc balance some men display a decrease in serum cholesterol and vitamin A, an increase in erythrocyte glutathione reductase stimulation index and folate, a decrease in sweat zinc and a maintenance of serum zinc levels, though some men display temporary decreases. Thus the minimal requirement for zinc in a conventional U.S. diet is probably about 3.5-4.0 mg daily. Multivarient analysis of data from 131 balance studies suggests that the dietary zinc requirement is strongly influenced by the level of dietary protein and phosphate. Average zinc requirement when dietary protein is 100 g and phosphate 1.5 g is about 12.5 mg daily. When levels of dietary protein and phosphate are lower, the dietary

requirement for zinc is lower. The findings also suggest that amounts of dietary fiber sources usually eaten in the U.S. probably have little impact on zinc requirement. On the other hand, preliminary findings suggest that increased dietary intakes of Maillard reaction products can impair intestinal absorption and retention of zinc. Thus, the level of intake of non-absorbable zinc binding ligands is probably an important factor influencing zinc homeostasis.

E. Iron nutriture is related to neurophysiological performance of adults fed conventional diets. Serum ferritin relates to EEG power and lateralization and also to certain indices of cognition. These relationships are evident when iron stores, indexed by serum ferritin, are within the normal range. Evidence of these relationships was obtained from cross sectional observations on volunteers entering studies in the human studies unit, from longitudinal observations on volunteers depleted of iron, and a cross sectional study of college students. As the latter study involved 70 individuals, the findings are probably generalizable to the population.

F. Consumption of 5000 Kcal diets containing about 1 g cholesterol and substantial amounts of polyunsaturated fat (PUFA) or saturated fat (SFA) by highly fit athletes had profound effects on serum cholesterol, as predicted by the Keys equation. When about 50% of energy was from SFA, serum cholesterol was about 240 mg/dl. When PUFA provided about 55% of energy, serum cholesterol was about 160 mg/dl. Retention of iron and zinc were significantly impaired and copper was unaffected when the PUFA intake was high. When SFA intake was high, retention of iron, zinc and copper were apparently normal. The effects on cholesterol were consistent with the literature. The effects of PUFA on mineral balance were quite surprising and cause one to wonder if PUFA affects lipid metabolism, in part, through changes in mineral metabolsim.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

DHHS Nutrition Research and Training Overview

By

Artemis P. Simopoulos, M.D.

DHHS NUTRITION RESEARCH AND TRAINING: OVERVIEW

Within DHHS, human nutrition research is supported by NIH, ADAMHA, FDA, and HRSA. In addition, NCHS and CDC carry out monitoring and surveillance programs that generate data of significance to the research effort. When necessary, CDC carries out research on analytical methods in nutritional biochemistry in order to improve the methods for the assessment of nutritional status of populations.

Table 1 indicates that in FY 1981 the Federal government spent $218 million on human nutrition research, research training, research manpower development, and research on public information and education. Of the $218 million expended on nutrition research, DHHS accounted for $160 million (73 percent) with NIH expending $148 million (68 percent of all Federal expenditures).

TABLE I

FY 1981 EXPENDITURES BY FEDERAL AGENCIES IN HUMAN NUTRITION RESEARCH, MANPOWER DEVELOPMENT, TRAINING, AND EDUCATION, BY AREA OF SUPPORT
(in Thousands of Dollars)

Agency	Extramural Research	Research Manpower Development	Intramural Research	Research Training	Research on Public Information and Education	Total	%
DOC	953					953	0.4%
DOD	28		1,653			1,681	0.8%
DHHS: NIH	130,814	1,310	9,893	3,709	2,775	[148,501	68%]
ADAMHA	4,861		633			[5,494	2.5%]
FDA	243		4,974*		175	[5,392	2.5%]
CDC					716	[716	0.3%]
HSA	67					[67	<.1%]
DHHS Total	135,985	1,310	15,500	3,709	3,666	160,170	73%
FTC						0	0%
IDCA-AID	2,783				926	3,709	2%
NASA	212		162			374	0.2%
NSF	1,298					1,298	0.6%
USDA	11,101		27,627		8,400	47,128	22%
VA			2,500		77	2,577	1%
TOTAL	152,360	1,310	47,442	3,709	13,069	217,890	
	70%	0.6%	22%	2%	6%		100%

* Represents 115 person-years of effort.

The nutrition activities of DHHS include research, training, education, regulation, nutritional status monitoring of the population, and food programs and their evaluation. The Department supports research and research training in nutrition that are essential for maintaining all of its nutrition activities. Such research includes:

Biomedical and behavioral research that is designed to improve the quality of life for all Americans through optimal nutrition. Biomedical and behavioral nutrition research will develop knowledge needed to promote and maintain health, as well as to prevent and treat disease.

Research on the determinants for assessing and monitoring the nutritional status of individuals and populations. Such research will enhance our ability to monitor the nutritional status of the population and to provide timely and appropriate intervention, as needed.

Research in food sciences to examine the nutrient composition of foods and improve our understanding of the safety, quality, and nutritional value of foods, diets, and the national food supply.

Research in nutrition education to enhance the nutrient composition of physicians, allied health personnel, nutrition educators, and the public.

Current DHHS nutrition research and research training concentrates on 11 critical areas: nutritional requirements throughout the life cycle; role of nutrition in the etiology of disease; prevention of disease; treatment of disease; food science; nutritional status of populations; technology transfer; international nutrition research; research training; nutrition education; and coordination.

In order to foster a comprehensive and effective program of nutrition research and training within DHHS, the Departmental Research Initiative in Nutrition (DRIN) was established in 1979. The principal thrust is to reinforce a coherent research program and to extend the growing trans-Institute cooperation in nutrition research to other DHHS agencies. NIH was designated as the lead sponsoring agency to develop the Nutrition Research Initiative, and the NCC Chairman was designed as the coordinator. To implement the DRIN, a committee with members from the six cosponsoring agencies (NIH, ADAMHA, FDA, HRSA, CDC, and NCHS) has been given the task of developing a cohesive program for the Department in order to best carry out this Nutrition Research Initiative. The committee has the following responsibilities:

- o to review and comment on the plans, execution, and results of research efforts, in order to refine and strengthen the Department's nutrition program;
- o coordinate research stemming from the Clinical Nutrition Research Units (CNRU's), nutrition research training and manpower development programs, and other nutrition research programs, and repre-

sent DHHS in interdepartmental activities relevant to nutrition research and training;

- o provide information and advice on the DHHS nutrition research programs to the directors of the agencies involved, to the Office of the Assistant Secretary for Health, and to the Office of the Secretary;

- o continuously evaluate research data and provide advice for the development of nutrition education materials for the public; and

- o plan and arrange for conferences, workshops, consensus development exercises, and reports as appropriate.

The Secretary, DHHS, inaugurated the nutrition research initiative with his keynote address at the "Conference on the Assessment of Nutritional Status," held at the NIH on September 16-18, 1981. The conference was cosponsored by the NIH-NCC, CDC and FDA. The objective of the conference was to highlight the current state of the art in the assessment of nutritional status. Emphasis was on the currently available methods and their technology, its adequacy and shortcomings; and most importantly, on the identification of research needs to develop adequate methods for nutritional assessment. Attention was given to the evaluation of the nutritional status of individuals with emphasis on the low birth weight infants, the elderly, and hospitalized patients, including surgical patients.

The second step in the implementation of the initiative was the "Workshop on Body Weight, Health and Longevity," cosponsored by the NIH-NCC and the CDC, held at the NIH on January 25-26, 1982. The conference participants concluded that overweight people tend to die sooner than average weight persons; this is particularly true for those who are overweight at younger ages. This effect of overweight on mortality is delayed, so that it is not seen in short-term studies. The recent analyses of the Framingham Heart Study data emphasize that obesity is a significant predictor for cardiovascular disease with smoking having an effect separate from that of overweight. Later in the program, Dr. Hubert will present a paper with some fascinating new data from the Framingham study.

In addition to the conferences, work sponsored under DRIN includes the joint PA, "NIH New Investigator Research Award (NIRA) in Nutrition--ADAMHA Special Notification for Research on Nutrition and Behavior." This PA had the support of NIH (NCI, NIADDK, NICHD, and NIDR) and a sister agency, ADAMHA. The National Institute of Alcohol Abuse and Alcoholism and the National Institute of Mental Health of ADAMHA joined NIH in encouraging new investigators to develop their research interests and capabilities in various aspects of nutrition and behavior. Much of the nutrition research supported by ADAMHA covers the areas of anorexia, bulimia, obesity, the effects of nutrients on behavior, and the effects of behavior on dietary intake and nutritional status. A more comprehensive presentation of ADAMHA's nutrition research program is planned for the JSHNR's second annual conference of Federally-Supported Human Nutrition Research Units.

NIH is the major agency in Federal government that supports research and training in nutrition as it relates to health maintenance, human development throughout the life cycle, disease prevention and disease treatment. My presentations on the NIH Extramural Program (following this presentation) and on the NIH Intramural Programs (later this afternoon) will give an in-depth look at nutrition research at NIH.

ADAMHA is comprised of three Institutes: the National Institute of Mental Health (NIMH), the National Institute on Drug Abuse (NIDA), and the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Their nutrition research programs focus on the biological, behavioral, and/or psychological factors involved in food and nutrition-related behaviors.

FDA's Bureau of Foods nutrition research program is directed toward research studies that will enable the Bureau of Foods to safeguard the nutritional quality of the nation's food supply, foster the application of modern nutrition principles to the dietary management of disease and injury, protect the public from fraudulent and/or harmful food products, and improve consumer understanding of food values and their importance to nutritional health. Such research is carried out to support FDA's mission to establish food fortification policies and regulations to ensure food safety, undertake initiatives to improve food quality, develop policies and regulations governing foods used for dietary management of patients with serious diseases and injuries, and support public and professional information and education efforts.

HRSA is the agency with leadership responsibility for general health service and resource issues relating to access, equity, quality, and cost of care. Although not a primary focus, nutrition research and special studies whose results have potential for transfer to health care delivery programs for populations served by HRSA programs are supported.

National Institutes of Health
Extramural Program in Nutrition Research

By

Artemis P. Simopoulos, M.D.

NATIONAL INSTITUTES OF HEALTH
EXTRAMURAL PROGRAM IN NUTRITION RESEARCH

The NIH nutrition research program constitutes the majority of the DHHS research, with 90 percent of its program for the support of extramural nutrition research carried out at various universities; in graduate science departments, principally departments of nutrition; and in medical, dental, and other health professional schools, especially schools of public health. The program is supported by all 11 Institutes and one Division, namely: National Cancer Institute (NCI); National Heart, Lung, and Blood Institute (NHLBI); National Institute of Dental Research (NIDR); National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK); National Institute of Neurological and Communicative Disorders and Stroke (NINCDS); National Institute of Allergy and Infectious Diseases (NIAID); National Institute of General Medical Sciences (NIGMS); National Institute of Child Health and Human Development (NICHD); National Eye Institute (NEI); National Institute of Environmental Health Sciences (NIEHS); National Institute on Aging (NIA); and the Division of Research Resources (DRR).

The Institutes with mandates in categorical diseases support nutrition research programs in their areas of responsibility in both the prevention and treatment of disease; namely, NCI on diet and cancer; NHLBI on diet and heart, lung and blood disorders; NIDR on nutrition and dental caries; and NEI on nutrition and various eye disorders. NIADDK, NICHD, and NIA support nutrition research particularly related to nutrient requirements relevant to the different stages of the life cycle and specific metabolic and genetic diseases, including a special program on TPN. Through studies in biochemistry, physiology, and cell biology, NIH supported research aims at elucidating fundamental mechanisms and at synthesizing the results into practical information on nutrition and diet that will assist the individual to develop normally, and to live a long and healthy life as is possible.

The Division of Research Resources (DRR) supports 75 General Clinical Research Centers in the United States. The research beds, laboratories, professional nursing, and dietary personnel that comprise each center are essential to clinical investigation in nutrition. These centers conduct clinical nutrition studies on atherosclerosis, cancer, diabetes, environmental health factors, hyperlipidemias, obesity, parenteral nutrition, and vitamins. In all, the dietary support personnel working in these centers number 236 full time equivalent, while 800 interns are trained there annually. Several of the 43 currently funded, clinical associate physicians are directly involved in clinical nutrition research. The team approach in clinical investigation at the centers allows the basic scientist, clinician, dietitian, and nurse to interact in developing systematic methods for nutrition research.

All of the NIH Institutes, except NIGMS and NINCDS, support intramural nutrition research. A presentation of the highlights of the NIH Intramural Research Program follows today's presentations of the nutrition research highlights of the NIH-supported Clinical Nutrition Research Units (CNRU's).

Nutrition is an important, crosscutting program area within the NIH. For this reason, the nutrition program is coordinated through the NIH Nutrition Coordinating Committee (NCC) that operates out of the Office of the Director and is advisory to the Director. The mandate of the Nutrition Coordinating Committee is to review, stimulate, and encourage the necessary support of nutrition research and training in order to better define the role of nutrition in the promotion of health, and the prevention and treatment of disease. A detailed description of the overall NIH nutrition program is published each year by the Nutrition Coordinating Committee as the Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training.

For FY 1981, the total NIH actual obligation in biomedical and behavioral nutrition research and training was $148,501,000. Table I presents the FY 1981 expenditures by category of support. Overall, NIH supports more than 1,600 research grants, program projects, contracts, and centers in nutrition.

The NIH nutrition program is presented in terms of 15 Special Interest Areas because of the scientific and political interest that has surrounded these particular aspects of nutrition research in the most recent past. These areas, presented in decreasing order of expenditures, are: Nutrition and Prevention of Disease, Nutritional Status, Behavioral Studies in Nutrition, Child and Infant Nutrition, Research on Vitamins, Epidemiological Research in Nutrition, Nutrition and Obesity, Nutrition and Genetics, Total Parenteral and Enteral Nutrition, Nutrition and Aging, Maternal Nutrition, International Research in Nutrition, Nutrition Education for Professionals, Nutrition Education for the Public, and Nutrition Education Research.

The NIH supports training in biomedical and behavioral nutrition research for both the extramural and intramural programs. Within the extramural program, two basic mechanisms are used for nutrition training support: training grants and fellowships. Table II summarizes the expenditures and number of persons who received training in FY 1981.

TABLE I

National Institutes of Health
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1981,
BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Extramural	Item	Number	Cost	Total Number	Total Cost
Research grants:	Regular	1,189	$ 70,245		
	Clinical trials	113	3,206		
	Total			1,302	$ 73,451
Program projects:	Regular	74	15,190		
	Clinical trials	5	769		
	Total			79	15,959
Contracts:	Regular	113	7,870		
	Clinical trials	58	8,555		
	Total			171	16,425
Centers:	Regular	92	12,034		
	Clinical trials	1	33		
	Total			93	12,067
General research support				260	13,136
Reimbursement agreements				16	1,319
Training:	Training grants	268*	3,159		
	Fellowships	36	549		
	Total			304*	3,708
Research Career Development Awards				34	982
New, Academic and Teacher Investigator Awards				64	1,560
Subtotal - Extramural					$ 138,608
Intramural					
Projects				95	9,193
Training				25*	700
Subtotal - Intramural					$ 9,893
TOTAL NUTRITION RESEARCH AND TRAINING - NIH					$ 148,501

* Number of persons

TABLE II

NIH TRAINING IN NUTRITION, FY 1981

Institute	M.D. Degree	Ph.D. Degree	Other Degree*	Pre-Doc	Total No. of Persons Trained	FY 1981 Obligations (Dollars in thousands)
EXTRAMURAL:						
Institute Training Grants:						
NCI	1	4	1		6	$ 270
NHLBI	3	38	1	8	50	1,165
NIDR		6	2	2	10	186
NIADDK	13	8		32	53	793
NIAID	1	3			4	10
NIGMS	27	1		64	92	473
NICHD	6	4	3	6	19	247
NIA			2	32	34	16
Subtotal	51	64	9	144	268	$3,159
Individual Fellowships:						
NCI		1			1	19
NHLBI	2	1			3	42
NIDR			2		2	54
NIADDK	2	14	1		17	251
NICHD	3	1			4	84
NEI		5			5	68
NIA		4			4	32
Subtotal	7	26	3		36	$ 549
EXTRAMURAL SUBTOTAL	58	90	12	144	304	$3,708
INTRAMURAL:						
NHLBI	6				6	$ 114
NIADDK	3	5			8	86
NICHD	9	2	1	—	11	500
INTRAMURAL SUBTOTAL	18	7	1	0	25	$ 700
NIH TRAINING TOTAL	76	97	13	144	329	$4,408

* Other Degree includes M.D./Ph.D, Ph.D./D.D.S., D.D.S, D.V.M., D.Sc., etc.

The NCC is the focus for the review and coordination of nutrition research and training priorities, and for the development of the NIH nutrition program. This focus minimizes duplication of effort among the Institutes and identifies areas where research, research training, and research manpower development in nutrition need to be advanced. This is accomplished through joint program announcements (PA's) and requests for applications (RFA's) developed by the Committee and sponsored by more than one Institute. Committee representatives are also encouraged to have their individual Institutes develop program announcements, requests for applications, and requests for proposals (RFP's). From FY 1977 through FY 1981, 68 PA's, RFA's, and RFP's in nutrition were published either individually or jointly by the Institutes. These announcements cover a wide variety of research and training interests ranging from the assessment of nutritional status, infant nutrition, human milk banking studies, overnutrition and obesity, mechanisms in food allergy, sodium and its role in the prevention and management of hypertension, to a New Investigator Research Award in nutrition developed jointly with the Alcohol, Drug Abuse and Mental Health Administration (ADAMHA) in the area of nutrition and behavior and Special Emphasis Career Awards that contain important nutrition components in obstetrical, perinatal, pediatric, cardiovascular, metabolic, and endocrinologic aspects.

A very significant contribution to the NIH's nutrition program was made in January 1979, when NCI, NIADDK, and NIA jointly published the RFA entitled "Core Grants for Clinical Nutrition Research Units (CNRU's)," which led to the funding of four CNRU's in FY 1979 and three additional units in FY 1980. This concept was developed by the NCC and formed the basis for the establishment of a new National Program in Clinical Nutrition Research. Although the CNRU program comprises a small portion of the total NIH nutrition program, its uniqueness in terms of financial support through the core grant mechanism and overall contributions to the NIH program makes it a most significant program.

The core grant for shared facilities promotes multidisciplinary interactions and tends to ensure that a given CNRU has multiple sponsors, both Federal and non-Federal, thereby reducing the likelihood that it will become unduly dependent on any one source for its continuing operation. Funding for educational programs of nutritional support services (patient care) are generally sought from sources other than NIH. The specific objectives of the CNRU are:

1. To create or strengthen foci in biomedical research institutions for multidisciplinary research in clinical nutrition in order to develop new knowledge about specific nutrients in health, human development, and the prevention and treatment of disease.

2. To strengthen training environments in order to improve the education of medical students, house staff, practicing physicians, and paramedical personnel in clinical nutrition.

3. To enhance patient care and promote good health by focusing attention towards clinical nutrition and generating nutritional information for the public.

A CNRU, at a minimum, must comprise the following seven components:

1. Research with human subjects and populations,
2. laboratory investigations,
3. research training,
4. shared facilities and research services,
5. education programs for medical students, house staff, practicing physicians, and paramedical personnel,
6. nutritional support services, and
7. public information activities.

In our attempts to identify program strengths and gaps, research needs, and recommendations for further coordination and planning in nutrition during the conference's final discussion session, particular attention should be paid to the CNRU concept, the research under way at the various CNRU's, and how this research relates to the nutrition research interests of the other agencies and departments represented at this conference. The seven CNRU Directors will present the nutrition research highlights of their particular CNRU immediately following this presentation.

In summary, although the Clinical Nutrition Research Unit Program is a small component of the overall NIH nutrition program (1.6 percent), the following presentations of the research highlights of the CNRU's will show their significant contributions to the NIH Program in Biomedical and Behavioral Nutrition Research and Training.

University of Alabama CNRU

By

Charles E. Butterworth, Jr. M.D.

Clinical Nutrition Research Unit
University of Alabama in Birmingham

SYNOPSIS

General Description (Overview): This unit consists of: (1) a central coordinating administrative staff; (2) a Clinical Nutrition Support Service for inpatients and outpatients; (3) Research Laboratories and (4) Diagnostic Laboratories. It functions as an integral component of the Department of Nutrition Sciences. There are 19 full-time faculty members in the Department (four MD, one MD-PhD, one MD-Dr PH, seven PhD, five MS-RD, one MA). Six of these receive partial salary support from the CNRU grant. In addition, a biostatistician, a clinical psychologist, and a pharmacist receive partial salary support from the grant and have joint appointments in Nutrition Sciences.

The overall goals of the CNRU are improved patient care and disease prevention; related goals include improved nutrition education and information exchange.

The broad thrusts and major identities of this CNRU include the following:

* Studies of hospital malnutrition and its prevention. (This includes awareness-promotion, identification of high-risk patients, development of clinical and laboratory assessment techniques, and ultimately the development of guidelines and staff for delivery of first-rate nutritional care).
* Role of nutrition in the etiology and prevention of cancer, especially the concept of localized vitamin deficiency.
* Feeding problems, including obesity, anorexia, bulimia, short bowel syndromes, home parenteral nutrition.
* Multiphasic screening for vitamin status assessment.
* Folic acid biochemistry and metabolism.

RESEARCH AREAS; ONGOING RESEARCH, RESULTS, HIGHLIGHTS

A. Nutritional Support of Seriously Ill Patients (Hospitalized and Ambulatory

1. Bacterial Contamination of Tube-feeding Formulas
Tube feeding formulas were cultured at the end of the infusion on every patient receiving this form of nutritional support during each of two separate 24-hour periods in a large teaching hospital.

   * Six of the 35 samples were contaminated with one or more coliform organisms (E. coli, Enterobacter sp., Citrobacter sp., Klebsiella pneumoniae). One contained over 20,000,000 cfu's/ml, 4 contained >100,00, 5 >1,000, and 6 >50 cfu's/ml. Therefore all 6 exceeded the allowable limit for pasteurized milk, according to conventional health department standards.

* Patients receiving formulas with >100,000 cfu's/ml had a significantly greater incidence of diarrhea ($p < 0.02$) than those receiving non-contaminated formulas.
* Locally-prepared and "manipulated" commercial formulas had significantly more contamination than unmanipulated commercial products which were generally <10 cfu's/ml at the end of the infusion.
* Although pneumonia due to aspiration of formula occurs not infrequently, the relative risk of aspirating contaminated formula has never been assessed.
* It is concluded that improved techniques for administration can significantly reduce the morbidity and mortality associated with the use of tube feedings.

2. Collaborative research with Dr. Pruitt of the Biochemistry Department and Dr. George Laven of this Department has concerned the reported effectiveness of extra substrate for the peroxidase system of cow's milk in prolonging shelf life. It has been found that human milk contains primarily myeloperoxidase, whereas bovine milk contains lactoperoxidase. In vitro addition of sodium thiocyanate in amounts comparable to those of saliva, along with a source of H_2O_2 such as sodium percarbonate markedly inhibit the growth of gram-negative organisms in human milk. A commercially available solid-phase enzyme system is also being investigated.

   Potentially important applications include use in infant-feeding formulas in developing countries, and in enteral feeding formulas for hospitalized patients.

3. It has been observed, in collaboration with Dr. V. Herbert and members of the Department of Medicine that 47 of 184 (25.5%) patients with Rheumatoid Arthritis had diminished levels of serum vitamin B12 (<175 pg/ml). This was significantly greater than in the general hospital population (15.9% of 977) and in a healthy control group (7% of 128). It is postulated that the radioassay using pure IF may not be detecting certain biologically active analogues in this population. (See Arth. & Rheum. Vol. 25, Supp 4, page S-116, April '82)

4. A prospective study of the frequency of metabolic complications of central venous alimentation has been completed (J.P & E Nutr 6:421-425, 1982). One hundred consecutive medical and surgical patients were studied over a 7-month period. At least one severe biochemical defect (outside the 99th percentile rank) was observed in 63% of the 100 cases. Septic complications occurred in only 4% of the 220 catheter insertions. We conclude that greater attention should be directed at the prevention of these complications through better professional management of nutritional therapy.

B. Nutrition and Cancer

1. Following the report by Wassertheil-Smoller, et al. (Am. J. Epidemiol 114:714, 1981) that vitamin C intake was significantly lower in a group of patients with cervical dysplasia than in a matched group of controls, we tabulated the folate content and ascorbate content of 127 food items. The folate data were from assays performed in this laboratory under a USDA contract. Vitamin C content of the same food items was derived from Agricultural Handbook #456. A highly significant correlation was found between the content of the two nutrients (r 0.34, $p < 0.001$).

   We conclude that diets low in ascorbate are likely to be deficient in folate as well. Thus the work of Wassertheil-Smoller et al. tends to corroborate work published earlier from this laboratory.

2. A study has been completed (in collaboration with Dr. John Carpenter of the UAB Comprehensive Cancer Center) concerning the activity of folic acid conjugase in plasma of patients with breast cancer. It was observed that plasma from 12 normal female subjects had a specific activity (mean $\pm$ SEM) of 0.93 ± 0.05 p mol/mg prot/min at pH 7.4. The comparable result in 12 women with clinically evident metastatic breast cancer was 1.79 ± 0.16 ($p > 0.001$) while 13 subjects with proven axillary node involvement had a value of 1.22 ± 0.12 ($p < 0.005$).

   Preliminary studies on specimens from 6 human breast cancers have demonstrated significantly greater conjugase activity than in normal adjacent breast tissue. It is postulated that increased conjugase activity causes increased folate turnover and localized folate depletion.

3. Data collection has recently been completed on 100 patients admitted to the hospital for surgical management of gynecological cancer (e.g. invasive carcinoma of cervix, uterus, ovary). Results of anthropometry, 3-day diet history, and blood levels of 8 vitamins are currently undergoing computerized statistical analysis.

C. Feeding Problems; Clinical Nutrition Support Service

1. During the past year the team provided formal consultations for 283 patients. In the ambulatory setting there were 515 patient visits, including 7 patients on home TPN.

2. All patients currently referred to the ambulatory clinic for a feeding problem (e.g. anorexia nervosa, bulimia, obesity) are seen by a team including physicians, a nurse, dietitians, and a clinical psychologist. One patient with bulimia was admitted for study on the Clinical Research Unit. Serial measurements of plasma tryptophan during periods of low or high-protein intake, or fasting did not correlate with perceived craving for food.

3. Dr. Weinsier recently spent two weeks in New York in collaboration with Dr. Van Itallie of the St. Luke's - Roosevelt Hospital Obesity Center, extracting data from records of 399 consecutively studied obese patients.

The data are being analyzed statistically in Birmingham. A number of interesting observations are beginning to emerge. Among these is the observation that obesity, per se, does not appear to contribute to the development of hypertension unless there is a genetic predisposition to hypertension.

D. Diagnostic Laboratory

1. During the past year a total of 9,239 vitamin assay determinations were performed on blood specimens from patients in University Hospital, the ambulatory center and others. Of this number 1,670 were separate, single assays while 841 were "screens". The latter consists of the following 9 determinations carried out on a single 8.0 ml Vacutainer ® of blood containing EDTA: plasma folate, B12, ascorbate, carotene, vitamin A; and in red cells the concentration of folate, and activity coefficients for thiamin, riboflavin and pyridoxine.

2. A method involving HPLC has been developed for assay of retinol, alpha tocopherol, and vitamins D-2 and D-3. The technique is available for use with both clinical samples and foods (including milk).

E. Nutritional Biochemistry Research Laboratories

1. The third in a series of analytical papers has been published by Eto and Krumdieck (Analytical Biochemistry 120:323 (March) 1982). Details are presented describing the use of reversed-phase HPLC to separate and quantitate picomole quantities of various one-carbon pools according to polyglutamyl chain length. The method is based on differential rates of cleavage at the C9-N10 bond to produce p-aminobenzoylpolyglutamates.

   It has been found that rat liver folate consists predominantly of formyl derivatives (44.3 $\pm$ 7.7%) with methyl derivatives comprising 36.7 $\pm$ 4.7%. In agreement with other investigators it was found that most intracellular folate is in the form of penta- and hexa- glutamates.

2. Nuclear Magnetic Resonance (NMR) spectra obtained in collaboration with Dr. Abu Khaled have demonstrated molecular alterations in vitamin B12 following exposure to low concentrations (10%) of butyl nitrite. This observation is believed to be of potentially great significance in connection with damage to epithelial surfaces (e.g. respiratory and digestive) by this and other oxidizing agents, including those of tobacco smoke. Profound localized alterations in vitamin B12 function, although transient, could be carcinogenic by damaging DNA. Similar damage to lymphocytes and immune mechanisms, (for example as seen in the current epidemic of "AIDS"), is also possible.

3. Drs. Krumdieck, Tamura, and Eto have completed a chapter entitled "Synthesis and Analysis of Pteroylpolyglutamates" for the 1983 edition of "Vitamins and Hormones". This involved an extensive literature review and inclusion of more than 190 references.

4. Studies are in progress regarding the role of zinc in the synthesis of pteroyl-polyglutamates; the role of folate coenzymes in methionine biosynthesis; the role of ethanol in hepatic carcinogenesis in rats; and the use of low methionine diets to control schizophrenic behavior in humans.

Medical College of Georgia CNRU

By

Elaine B. Feldman, M.D.

Clinical Nutrition Research Unit
The Medical College of Georgia
Elaine B. Feldman, M.D., Principal Investigator

Overview of Ongoing Activities

The broad thrust of the CNRU at the Medical College of Georgia is to provide the research arm of the Georgia Institute of Human Nutrition (GIHN). The purpose of the GIHN is to enhance and coordinate nutrition research with a primary thrust in the role of nutrition in the etiology of important diseases, in this region predominantly cardiovascular disease. We are focusing on research in the risk factors of dietary and genetic hyperlipidemias, trace minerals, and obesity with a view to prevention and treatment. A secondary thrust of our clinical component is to define effects of specific diseases and associated stress to alter nutritional requirements of hospitalized patients, especially of fuel, protein and trace minerals and improve their nutritional therapy.

Georgia is in the "strokebelt" of the U.S. with a high incidence of hypertension, and cerebral and coronary artery disease. We are particularly interested in the relationship of dietary lipids (fats, sterols) and trace minerals (selenium) in the etiology of these disorders. Our pilot projects emphasize clinical investigation using the facilities of the core laboratories. These projects are selected by open competition with review by the Executive Committee. This year we added a statistician to review the protocols submitted regarding data analysis and appropriate sample size. The core laboratory is CAP accredited. Measurements are provided of lipids, lipoproteins, apoproteins, nitrogen, proteins, amino acids, B vitamins by enzyme dependent activity, vitamins A and E, selenium and glutathione peroxidase. This year we are developing indirect calorimetry, zinc and copper analyses and quantitative assays of specific apoproteins and LCAT. The core laboratory was directed by a nutritional biochemist who recently moved; a replacement is being recruited actively. In the meantime an assistant research scientist, Dr. Richard Carroll, with three years postdoctoral training in the SCOR program at Bowman-Gray, was recruited for the lipid laboratory and is carrying out independent research and expanding the methodologic capability of that laboratory. His research relates diet and genetics to hyperlipoproteinemia in patients and in Rhesus monkeys fed atherogenic diets.

Research

Atherosclerosis. Plasma cholesterol, HDL cholesterol and triglyceride levels have been determined in MCG medical students since 1972. Students are initially screened as freshmen and repeat determinations are made during their senior year. Approximately 34% (n=60) of the

senior class of 1982 participated voluntarily. Mean values in the survey were: total cholesterol 183 mg/dl; HDL cholesterol 46 mg/dl; and triglycerides 90 mg/dl. Only 7% of the group showed elevated levels (cholesterol >230 mg/dl and/or triglycerides >150 mg/dl). The purpose of the screen is to detect hyperlipidemia at an early age, offer treatment to students with elevated lipid levels, and use the data as part of a continuing study on changes in circulating lipids over time in a young population. Another important impact of this study is to teach young future physicians about lipids and their significance as risk factors in cardiovascular disease.

A multicenter collaborative study of an experimental lipid lowering drug, fenofibrate, is underway. Twelve patients with types 2A and 2B hyperlipoproteinemia are enrolled in a six-month, double-blind study of fenofibrate vs. placebo followed by an open-label, six-month treatment period to evaluate long-term efficacy, safety and tolerance. The study includes diet counseling and monitoring and measurement of lipids, lipoproteins, hemogram, urinalysis, and blood chemistries. One adverse reaction (skin rash) has occurred.

The National Heart Lung and Blood Institute has a non-human primate resource contracts program to breed, model and supply non-human primates for studies of atherosclerosis and dyslipoproteinemia. Dr. Elaine Feldman was a participating investigator in the Litton Bionetics contract this year and was responsible for evaluation of their clinical and lipoprotein data. She is proposing a pilot study utilizing Rhesus monkeys from the Litton colony to provide a data base to improve the breeding of the diet-induced atherogenic model. Family groups of Rhesus characterized as hypo- or hyper-responders to a high cholesterol, high fat diet will be evaluated to determine whether they behave similarly when fed a defined diet with less cholesterol and more saturated fat. Plasma and lymph lipoproteins will be characterized in monkeys fed these diets and the stock diet to identify mechanisms controlling dietary response. Measurements will be made of total and esterified cholesterol, phospholipids, triglycerides, and apolipoproteins in samples from the monkeys ingesting each diet. Three family groups differing in responsiveness and HDL levels when fed the test diet (high, average, low) will be studied. Age and sex influences will be observed. Genetic and dietary effects will be compared in the more and less susceptible monkeys with special attention to effects on plasma and lymph lipoproteins and apoproteins. These results may provide leads to an alternate plan of colony development and maintenance for a better non-human primate model for atherosclerosis. Clues may be provided to biologic processes controlling diet-induced hyperlipoproteinemia. Characteristics of monkeys may be identified to pinpoint subjects for later noninvasive testing in vivo for development, progress and severity of atherosclerosis.

Selenium. Selenium (Se) concentrations are significantly lower in the soil of the coastal plain (southern two-thirds) of Georgia compared to the iedmont. Epidemiologic studies reveal an increased incidence of hypertension and cerebral, renal, and coronary vascular disease in subjects residing in environments with low Se concentrations, compared to high Se environments. Surveys of healthy Georgia residents living in the coastal plain indicate that Se levels in plasma and erythrocytes (mean plasma Se=104 ng/ml; mean erythrocyte Se=158 ng/ml) are lower than the reported values for most U.S.A. populations. Despite these low values, lack of functional significance is suggested by glutathione peroxidase activities within the normal range. A survey of pregnant women revealed a 20% decline in plasma and erythrocyte Se levels during the second and third trimesters of pregnancy, compared with first trimester values. In subjects whose pregnancy was complicated by anemia, plasma Se was low throughout gestation and erythrocyte Se declined 20% after the first trimester. Fetal outcome, as measured by birthweight and gestational age, was unrelated to maternal Se status. A survey of malnourished hospital patients indicated that 13 of 24 had plasma Se values less than two S.D. below the mean value obtained for healthy subjects from this geographic region (mean values of 24 malnourished patients: plasma Se=63 ng/ml, erythrocyte Se=132 ng/ml). In the patients with plasma Se less than the 5th percentile of normal, RBC glutathione peroxidase levels were significantly correlated. Ongoing studies will determine the association between low Se status and signs of Se deficiency, various disease states, and general indices of malnutrition.

Prostaglandins influence both renal blood flow and smooth muscle vascular tone and may be implicated in the etiology and/or treatment of hypertension. Se is involved in prostaglandin metabolism. Currently, a study is underway to examine Se-essential fatty acid interactions on the generation of prostaglandins and the development of hypertension in the spontaneously hypertensive rat model.

Cancer. Cancer patients may be predisposed to infection as a result of malnutrition, chemotherapy and/or cancer per se. Preliminary studies have demonstrated an inhibitor of neutrophil function (chemotoxis and phagocytosis) in the serum of malnourished cancer patients. Serum inhibition correlated with nutritional status and was reversed by 1-3 weeks of enteral nutritional support. Other investigators have identified heat-stable serum inhibitors, associated with polymeric IgA, but an association with malnutrition was not sought. This study (funding pending) will examine: 1) the prevalence of inhibitor; 2) the correlation of inhibitor with numerous parameters including nutritional status, clinical features, lymphocyte function, incidence of infection, etc.; 3) the effect of nutritional intervention on inhibitor presence and risk of infection; and 4) additional characteristics (chemical and physiologic) of the inhibitor. Aims 2 and 3 will be conducted exclusively in a population with squamous cell lung cancer receiving uniform chemotherapy. Subjects with other tumor types or therapies will be

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included in aims 1 and 4. This study will test the hypotheses that a neutrophil inhibitor is a determinant of infection in malnourished cancer patients and its elimination by nutritional support lessens the risks of anti-cancer therapy.

Retinoids have been demonstrated to have substantial anti-cancer effects, but adverse effects have limited their clinical application. The National Cancer Institute indicated an interest in the ability of β-carotene to inhibit carcinogenesis. A study proposes to examine the ability of β-carotene to inhibit the development of bladder cancer in a high-risk population. The study population will consist of 600 present and past employees of a chemical company that produced β-naphthylamine, a known bladder carcinogen. Beta-carotene vs. placebo will be administered in a double-blind fashion with blocking according to age, race and sex. This investigation will involve collaboration of several disciplines including occupational medicine, epidemiology, biostatistics, pathology, urology, nutrition and health education. If β-carotene demonstrates a positive inhibiting effect of carcinogens, the implication regarding cancer prophylaxis will be major.

Inborn errors of metabolism. A variety of inborn errors of metabolism have been studied with greatest emphasis on the dietary management of phenylketonuria and on seizure disorders. Investigation of the effects of hyperphenylalaninemia on myelin metabolism in the animal model is underway. The hyperornithinemia syndrome is also under study.

Folate-anticonvulsant interactions. Interactions between anticonvulsants and folates are well documented. Although folate deficiency is common in patients on chronic anticonvulsant therapy, folates in large doses are epileptogenic. Thus it cannot be assumed that folate supplementation is safe. Preliminary studies have demonstrated that rats treated with carbamazepine and valproate develop apparent folate deficiency. Rats treated with phenytoin have decreased liver and brain folate levels despite normal plasma levels. Folate supplementation of rats increased the apparent recovery time after electroshock induced seizures. This study will continue to characterize seizure/anticonvulsant/folate interactions in the rat model. The effects of seizures, anticonvulsants, and their combination on folate-dependent enzyme activities and the composition of the folate-bound one-carbon pool will be examined in rat brain. Folate-mediated one-carbon transfers will also be assessed by studying the metabolism of radiolabeled serine.

Methionine metabolism in schizophrenics. Methionine has been shown to exacerbate the psychoses of some schizophrenics; the catabolism of the methyl group of methionine to CO_2 exhibits a different kinetic profile in these patients compared to normal subjects. This study will examine in vitro methionine catabolism by leukocyte preparations obtained from 1) untreated schizophrenics during their first psychotic episode; 2) schizophrenics who have been treated with anti-psychotic drugs for

3-4 weeks; and 3) normal subjects. This design will determine the incidence of altered methionine catabolism and whether these alterations are pharmacologically induced.

Vitamin B_6. The mechanism of intestinal absorption of vitamin B_6 in the rat is being investigated. Pyridoxine-HCl(PN) and pyridoxal-5'-phosphate (PLP) have been used as representative nonphosphorylated and phosphorylated forms of the vitamins, respectively. In vitro everted sacs and in vitro perfused segments have been used to assess PN absorption. PN crosses the mucosal membrane by a process most consistant with passive diffusion, and a portion is then phosphorylated and subsequently hydrolyzed in the intestinal mucosa by pyridoxal kinase and alkaline phosphatase, respectively. One effect of this metabolism is compartmentalization of absorbed vitamin and delay in serosal exit (transmural absorption). In vivo perfused segment studies suggest that intracellular metabolism may also enhance PN mucosal uptake at low intraluminal concentrations under continuous perfusion conditions.

PLP luminal disappearance has been studied in the in vivo perfused segment model. Studies to date indicate that disappearance is largely due to alkaline phosphatase hydrolysis. Disappearance is saturable, inhibited by high pyridoxamine-5'-phosphate, inorganic phosphate, or L-phenylalanine intraluminal concentrations and correlates with perfusate alkaline phosphatase activity and net water absorption.

Pilot Projects. Pilot projects initiated this year or continuing from last year include: 1) a study of the effect of maternal dietary fat intake on fetal lung maturation in human subjects. In this study the dietary intake of pregnant women scheduled for repeat Cesarean section is evaluated and classified according to content of total fat, saturated fat, polyunsaturated fat and related to fetal lung maturation determined by amniocentesis. 2) Maternal protein nutrition is being studied in relation to fetal growth and retardation. The statistical analysis of nutritional status in normal vs. small for gestational age infants is under scrutiny. We have demonstrated some significant differences in levels of plasma and particularly RBC selenium in pregnant women. 3) Selected amino acid requirements if leukemic cells are under investigation in order to develop appropriate chemotherapy utilizing nutritional requirements of these cells. 4) Selenium balance in the dependent elderly is under assessment with and without supplementation. Platelet glutathione peroxidase levels will be followed and platelet aggregation. 5) A variety of parameters including the enhancement of delayed hypersensitivity by topical zinc are being evaluated as possible predictors of functional zinc status in human subjects. 6) Plasma amino acid profile (HPLC) and energy balance (indirect calorimetry) are being used to develop a nutritional regimen for patients undergoing total parenteral nutrition in an attempt to "tailor make" the nutritional solution rather than rely on routine formulas.

Vanderbilt University CNRU

By

Harry L. Greene, M.D.

VANDERBILT NIH SUPPORTED CNRU

The Vanderbilt CNRU was formed three years ago. Although nutrition has been an important ingredient in the Vanderbilt curriculum for more than fifty years, it has been primarily at the basic science level. In fact, the Division of Nutrition has been in the Department of Biochemistry. For this reason, nutrition per se has not been well correlated with patient care. Formation of the CNRU provided resources to achieve two major goals: 1) establishment of core facilities for laboratory, clinical, computer and administrative activities which could be lized in a cohesive manner and directed toward patient needs, and 2) a mechanism to support clinical nutrition research where positive results could be directly and immediately obvious.

Since there was no active clinical nutrition program at Vanderbilt, the organizational structure and activities had to be initiated from the ground level. However, because of the wealth of nutritional expertise and interest at Vanderbilt in Biochemistry and Dietetics, as well as a recognized need for clinical nutrition throughout the medical community, the CNRU has been able to focus on a larger number of individuals to meet the goals of the center. We have recently moved into newly renovated space of more than 3,000 square feet and are beginning several new and innovative clinical research projects in nutrition. All indications point to a highly successful program in clinical research which permeates all areas of clinical medicine with projects in Obstetrics and Gynecology, Surgery, Medicine, Pediatrics, and the Veterans Administration Hospital.

I. Research Activities

A. A rapid screen for malnutrition for hospitalized patients. The aim of this project is to devise a rapid screen for all hospital admissions who are at risk for malnutrition. The methods are testing two techniques: 1) a computerized laboratory screen of all routine laboratory tests, and 2) a brief questionnaire filled out by patients at the time of admission. The project data included 37 variables on 2,476 patients and resulted in a substantial data base (over 90,000 data values). Results indicate that an inexpensive computerized program available in most hospitals can be modified to identify patients with biochemical evidence of risk of malnutrition. In addition, a short patient questionnaire will identify 97% of all malnourished patients.

B. Nasogastric feeding at home in oat cell cancer patients. The goal is to determine the feasibility of maintaining or increasing weight in patients with oat cell carcinoma. Thus far, all patients are able to tolerate home nasogastric feeding. Six patients followed for more than one month either maintained their pretreatment weight or gained up to 10% ideal body weight.

C. Micronutrient metabolism in patients with essential fatty acid deficiency. The goals of this project are to determine the effects of fatty acid deficiency, the relationship between fatty acid levels and micronutrients, and the possibility that deficiency of copper or zinc might alter the rate of conversion of linoleic to arachadonic acid. Although many patients show deficiencies of a number of micronutrients, there is no obvious correlation between zinc and/or copper and a lack of formation of arachadonic from linoleic acid.

D. Trace elements in chronic renal disease. The goal of this project is to determine the incidence of zinc and copper deficiency in patients with chronic renal failure and alternatively evaluate the effects of zinc and/or copper supplementation. Three types of patients are being studied in

three separate protocols: 1) children who will later receive renal transplantation; 2) adults on hemodialysis; and 3) children and adults receiving chronic ambulatory peritoneal dialysis (CAPD). The first study suggests that the incidence of symptomatic zinc deficiency is about 20% and following transplantation, all children should receive zinc supplements. Second, adults on hemodialysis have low serum zincs but show no substantial benefit from supplementation. Third, CAPD patients may lose substantial zinc and copper, particularly with peritonitis.

E. Nutritional intervention in the moderately malnourished patient. The goal of this project is to establish criteria for moderate malnutrition and to determine if nutritional intervention will affect the outcome of surgical admissions to the Veterans Administration Hospital. Difficulty in defining moderate malnutrition has delayed the progression of this study.

F. Zinc and copper requirements in infants and children requiring special nutritional support. The goals of this study are, first, to determine if standard supplements of zinc and copper can be given to most infants and children requiring TPN or formula feedings, and if special disease states alter the needs from one patient to another, and, second, to determine what these needs are for children and infants. Studies indicate that not only does disease alter requirements, but the age of the child imposes substantial modifications in these requirements. The most difficult area of investigation is in the very small premature infants whose needs are substantially different from other patients and where controlled studies are exceedingly difficult.

G. Nutritional changes in patients undergoing coronary artery bypass surgery. This study was designed to examine 1) the nutritional status of patients admitted for CABVG, 2) the changes in nutritional parameters in the ten days after this reasonably well-controlled procedure, and 3) any correlation between these changes and operative or post-operative complications. To date, the nutritional status does not seem impaired and there is a very low incidence of complications in spite of the finding that protein synthesis is depressed.

H. Breast milk and micronutrients. This project involves the determination of zinc, copper, vitamins A, C and E in the milk of mothers delivering preterm for seven consecutive weeks post-delivery. Since zinc deficiency was found in several pre-term infants consuming exclusively breast milk, it was not surprising to learn that zinc content of breast milk decreases progressively during lactation. Secondly, oral supplementation of zinc does not appear to alter breast milk zinc in lactating mothers. It appears that pre-term infants need zinc supplementation if exclusively breast fed after four months of age.

I. The antibacterial effect of zinc and copper in dialysis fluid. This study was undertaken to assess the value of adding zinc to peritoneal dialysis fluid to prevent development of deficiency and subsequent infection. Bacterial replication in effluent peritoneal dialysis fluid was significantly reduced by the addition of zinc and copper sulfate in near physiological concentrations. When both compounds were added, the antibacterial effect was greater than predicted by the summation of each alone. As uremic patients are frequently zinc-deficient and copper losses in dialysate exceed those in urine, peritoneal dialysis causes increased zinc and copper losses. In addition, zinc absorption appears depressed in patients with uremia. This study should provide data to prevent deficiency of zinc and copper and simultaneously decrease the infection rate in patients requiring hronic ambulatory peritoneal dialysis.

J. Derivation of normal values from Red Cross blood. Since the literature does not provide normative data for micronutrients in individuals of all ages, the goal of this project is to evaluate all micronutrient parameters by age and sex with approximately 20 data points in each ten year period.

K. Use of an elemental diet in treatment of cystic fibrosis. This protocol is designed to investigate the effects of nocturnal nasogastric tube feedings of an elemental formula on the nutritional status (determined by anthropometric and biochemical measurements) and pulmonary function of children with cystic fibrosis. Dramatic improvements in strength, growth and general well being are induced by the three months of feedings and persist for an additional two months before reaching baseline levels.

L. Plasma amino acids after intravenous administration of the test solution (F-14) and L-Cysteine-HCL to pediatric patients requiring total parenteral nutrition (TPN). This project is designed to produce an amino acid solution for use in children which would produce a plasma amino acid pattern similar to that in the plasma of breast-fed infants. After testing four separate mixtures of amino acids, preliminary findings indicate that the current test solution achieves the indicated goal.

M. Concentration of taurine, carnitine, and amino acids in pre-term and full-term human milk. This project will evaluate the nutrient content of milk samples from mothers delivering at term as well as pre-term for several weeks post delivery.

II. Laboratory

The core laboratory component is supported to provide for core clinical projects. Virtually all vitamin measurements are available, as well as amino acid and trace mineral assays. Methodology is being tested and improved in an effort to obtain the most accurate and reproducible results as well as to reduce the volume of samples required for the assays. In addition, the laboratory personnel are actively involved in teaching of medical students and in organization of a laboratory booklet for instruction of laboratory methods for vitamin assays.

III. Biomedical Engineering (Data Management)

The CNRU Data Management and Analysis Core is operated by the Division of Biomedical Engineering Services (BMES). The activities of the BMES staff have been involved in working with CNRU project investigators to review and develop experimental designs, design schemes to support the creation of computer data bases, to perform data entry and data retrieval, to select and execute data analysis procedures, and to design special programs when problems have required such. Also, training has been supplied to investigators and their staffs so that they could use computer technology (especially the CLINFO system) on their own.

The computer technology employed by the BMES involves a unique hierarchy of computer systems. CNRU investigators are provided with the use of the BMES CLINFO system, which is a computer system developed by the NIH to meet the data management and data analysis needs of clinical research. In cases where needed, the CLINFO data bases are transferred through direct communication to the DEC-10 which is the Vanderbilt Campus Central Computer, where more advanced analysis procedures are easily obtained.

For the current reporting period, the data analysis core staff have assisted the various phases of experimental design, data management, and the data analysis on thirteen separate CNRU-sponsored research protocols.

IV. Education

Nutrition Center seminars are regularly conducted throughout the academic year. Topics range from basic scientific research and clinical research to

international nutrition surveys. Additional lectures include inservice conferences to pediatric and oncology nurses, presentations to nephrology rounds, dietetic interns and nursing students. An elective course in nutrition is offered to nursing students, summer electives are available to medical students, and one-month clinical clerkships are available to final year students. Residents in medicine attached to the primary care unit spend two mornings per week with the CNRU during a four-month rotation. Dietetic interns continue to rotate through the CNRU. Clinical and laboratory sessions have been incorporated into the Introduction to Nutrition course for first-year medical students (organized by Dr. H. Broquist, Department of Biochemistry) and several other lectures have been given. Teaching continues on an informal basis to residents involved with patient consultations. Lectures have been given to the American Society of Parenteral and Enteral Nutrition, the American Cancer Society Nursing Symposium, the three-state Dietetic Association in Washington, staff at the Nashville Kennedy Center for mentally retarded, local public health nurses, a nutrition conference at Meharry Medical School, and to students involved with the summertime Appalachia Health Project. Members of the CNRU participated with the Medical College of Georgia in the third Annual Frontiers in Nutrition Conference at Hilton Head. Through the Vanderbilt University Office of Public Affairs, articles have appeared in the lcoal newspaper describing the role of tube feeding at home in cystic fibrosis. During Nutrition Month, Ms. Folk was interviewed on a local TV station on nutrition support in chronically ill patients. A feature in RD, a dietetic publication, describes the structure and role of the CNRU. A bi-monthly regular newsletter containing current advances and practical advice on nutrition support is written and circulated to the VUH staff.

V. Patient Care

Nutrition center staff are available to the hospital staff for consultations. The growing number of consultative requests not only has provided substantial interaction with physicians, dietitians, nurses and other health care personnel, but also has stimulated the clinical faculty to institute a formal nutrition support service. This support service will be hospital funded and located contiguous with the CNRU.

The nutrition support team, which is to be implemented in January of 1983 under the umbrella of the CNRU, calls for hospital support for a dietitian and nurse with a faculty M.D. and a full-time pharmacist. The entire staff will be phased in over a year. The Nutrition Support Service will provide greater access to patients with research potential.

Patient care at Vanderbilt, subjectively, appears substantially improved with regard to the recognition and treatment of nutritional problems since the formation of the CNRU. There is clearly a closer liaison with attending staff which has resulted in modification of basic TPN solutions and an increased use of enteral feeding including home enteral feeding. The CNRU staff is actively involved in TPN audits, new product and equipment evaluations, and there is increased utilization of CNRU staff as a resource for teaching and patient onsultations.

Recent Publications

1. Rapidly declining serum albumin values in newly hospitalized patients: Prevalence, severity, and contributory factors. JPEN 6:143-145, 1982.
2. Intravenous lipid emulsions and human neutrophil function. J Pediatr 99:913-916, 1981.
3. Home tube feedings: General guidelines and specific patient instructions. Nutritional Support Services 2(6):18-22, 1982.
4. Nutritional management of Type I glycogen storage disease. In Textbook of human nutrition: Clinical and biochemical aspects, Philip JG (ed). The American Association for Clinical Chemistry, Washington, DC, p. 383-397, 1981.
5. Nasogastric tube feeding at home: A method for adjunctive nutritional support of malnourished patients. Am J Clin Nutr 34:1131-1138, 1981.
6. Nutritional support of the sick infant. Pediatr Ann 10:63-79, 1981.
7. Panel report on nutritional support of pediatric patients. Am J Clin Nutr 34(6):1223-1234, 1981.
8. Human milk and breast feeding: An update on the state of the art. Pediatr Res 16:266-271, 1982.
9. Promotion of breast feeding: Recommendations of the Councils of the Society for Pediatric Research (SPR) and the American Pediatric Society (APS) and of the American Academy of Pediatrics (AAP). Pediatr Res 16:264-265, 1982.
10. A controlled comparison of continuous versus intermittent feeding in the treatment of infants with intestinal disease. J Pediatr 99:360-364, 1981.
11. Zinc deficiency in a premature fed exclusively human milk. Am J Dis Child 136:77-78, 1982.
12. Dietary dependent carnitine deficiency as a cause of non-ketotic hypoglycemia in an infant. J Pediatr 99:551-555, 1981.
13. Elevated cholesterol and bile acid synthesis in an adult patient with homozygous familial hypercholesterolemia: Reduction by a high glucose diet. J Clin Invest 68:1166-1171, 1981.
14. More sensitive flameless atomic absorption analysis of vanadium in tissue and serum. Clin Chem 1:79-82, 1982.
15. Fetal alcohol syndrome: Inhibition of placental zinc transport as a potential mechanism for fetal growth retardation in the rat. J Lab Clin Med 100:45-52, 1982.

In Press

1. Nutritional aspects in management of biliary atresia. Proceedings of the International Conference on Extrahepatic Biliary Atresia, November 1981, Cornell University Medical College, Manhasset, New York.
2. A pathophysiologic approach to the dietary management of patients with protracted diarrhea and malnutrition. Proceedings of the Symposium on Nutritional Management of the Seriously Ill Patient, November 1981, Bristol-Myers Company, New York.
3. Response of the bowel to injury and the transition from parenteral to enteral feedings. In Proceedings of Cutter Laboratories Symposium "Parenteral Nutrition of the Pediatric Patient", February 1-2, 1982, ACTA Med Scan, Carmel, California.
4. Bidirectional Zn fluxes across the small and large intestine of diabetic rats. Life Sciences.
5. Fetal alcohol syndrome: Failure of zinc supplementation to reverse the placental defect of zinc transport. Pediatr Res.

Memorial Sloan-Kettering Cancer Center,
New York Hospital-Cornell Medical Center and
the Rockefeller University CNRU

By

Richard S. Rivlin, M.D.

SUMMARY OF RESEARCH IN PROGRESS OF THE CLINICAL NUTRITION RESEARCH UNIT (CNRU) OF MEMORIAL SLOAN-KETTERING CANCER CENTER, NEW YORK HOSPITAL-CORNELL MEDICAL CENTER AND THE ROCKEFELLER UNIVERSITY

Richard S. Rivlin, M.D. Principal Investigator
John T. Pinto, Ph.D. Assoc. Program Director
Renata Laqueur, Ph.D. Program Manager

November 1, 1982

The increasing importance of nutrition as a discipline has been recognized at Memorial Sloan-Kettering Cancer Center and in 1979 a new Nutrition Service (comparable to a division) was created in the Department of Medicine. In addition, a new Division of Nutrition was established at New York Hospital-Cornell Medical Center. To unify and coordinate the increased efforts in nutrition, Dr. Richard S. Rivlin was recruited to serve as the Chief of both Divisions, and to work together with certain investigators at The Rockefeller University who also shared interests in nutrition.

The three collaborating institutions joined together to apply for a CNRU in order to build a united and coherent program in nutrition. The Clinical Nutrition Research Unit Grant was awarded starting on September 1, 1980. These united efforts received further strengthening by the award of an "Interinstitutional Nutrition Research Training Grant" starting September 1, 1981, to provide support for the training of young physicians and scientists at the three participating institutions.

The Principal Investigator in 1981 received the Grace A. Goldsmith Lecture Award of the American College of Nutrition as a physician "who has uniquely combined basic investigations in nutrition and endocrinology with their application to clinical medicine especially for outstanding research regarding the hormonal regulation of amino acid and vitamin metabolism."

In terms of the major areas of themes of research, these projects can be classified as follows, with brief summaries attached:

a. Cancer and Nutrition
b. Metabolism and Diabetes
c. Nutrition and Immunology
d. Nutrition and Burns
e. Nutrition and Pharmacology
f. Lipids
g. Nutrition and Brain

The Directors of the five CNRU Core Laboratories are as follows:

Biophysics Core Laboratory - R. E. Bigler, Ph.D.

Immunology Core Laboratory - C. Cunningham-Rundles, M.D., Ph.D.

Lipids Core Laboratory - E. H. Ahrens, Jr., M.D. and D. J. McNamara, Ph.D.

Mass Spectrometric Core Laboratory - F. H. Field, Ph.D.

Metabolism and Metals Core Laboratory - N. Alcock, Ph.D.

a. Cancer and Nutrition (N.W. Alcock [MSKCC], R. Bigler [MSKCC], M.F. Brennan [MSKCC], J. Daly [MSKCC], J.J. DeCosse [MSKCC], S.E. Lowry [NYH], R.S. Rivlin [MSKCC], J. Roberts [MSKCC], N.H. Sarkar [MSKCC], M. Shike [MSKCC], and M.E. Shils [MSKCC])

The overall objective of these studies is to explore the derangements in metabolism which occur in cancer both in animals and in man, to determine the mechanisms causing weight loss, anorexia, and cachexia, and to develop optimal methods for preventing and treating the nutritional disturbances which result in cancer. In experimental animals, studies are exploring the role of serotonin in regulating appetite and satiety employing a serotonin-depleting enzyme. Other studies in experimental animals are determining whether riboflavin deficiency affects subversion of T-cells by syngeneic tumor, and prostaglandin metabolism in normal and neoplastic tissues, while related investigations are concerned with the effects of vitamin A nutriture and calorie restriction upon the incidence of murine mammary tumors, the expression of murine mammary tumor virus genes and hormonal status. These studies are concerned with elucidating the metabolic role of retinoids (synthetic vitamin A compounds). Clinical studies are concerned with the influence of total parenteral nutrition on glucose and amino acid turnover, the development of severe bone disease, and the development of selenium deficiency. Therapeutic approaches are aimed at deciding the optimal methods for nutritional rehabilitation of patients with head and neck cancer. Dynamic studies of zinc metabolism in man will now be feasible following the preparation of short-lived isotopes of zinc. Other investigations are concerned with the relationship of psychotropic drugs to riboflavin metabolism in older patients.

b. Metabolism and Diabetes (F. Adebonojo [NYH-CMC], A. Drexler [RU], F. Field [RU], D. Jacobs [MSKCC], L. Jovanovic [NYH-CMC], H Katzeff [NYH-CMC], C. Peterson [RU], and L. Resnick [NYH-CMC])

The overall objective of these investigations is to explore relationships between nutrition and endocrine disturbances, including diabetes growth failure, hypertension, obesity, and other disease states. One phase of these studies is involved with investigating immunological changes in well-controlled pregnant diabetics versus uncontrolled pregnant diabetics. Other studies are evaluating 3-methylhistidine as an index of protein balance in normal and diabetic subjects, particularly pregnant individuals, and in patients with weight loss secondary to metastatic cancer. The hypothesis that growth failure associated with the treatment of childhood malignancies involves both absorption defects in the GI tract as well as significant derangements in the cellular metabolism of some essential

nutrients is being tested in children with acute lymphoblastic leukemia, lymphomas, and retinoblastomas. In other studies, the effects of magnesium depletion upon the renin-angiotension-aldosterone system as well as on parathyroid hormone and calcium metabolism are being determined. Other endocrine-nutritional interrelationships under study at present include the effects of B-adrenergic stimulation on peripheral thyroid hormone production and the components of energy expenditure in man, and a possible potential therapy for infection-induced nephrolithiasis.

c. Nutrition and Immunology (C. Cunningham-Rundles [MSKCC] and S. Cunningham-Rundles [MSKCC])

The all over objective is to investigate the molecular aspects of local and systemic humoral immunity in relation to nutrition. Patients studied include those with IgA deficiency, hypogammaglobulinemia, inflammatory bowel disease and atopy. Major findings were as follows: (a) as casein content of milk decreased, anti-casein binding increased. Naturally occurring anti-idiotypic antibodies have not previously been demonstrated in human sera. Therefore, these experiments provide evidence of a unique model which may be used to explore the network theory of immunoglobulin regulation in humans; (b) the chronic excessive absorption of many food proteins, leading to the formation of antigen-antibody complexes and autoimmunity; (c) Zn deficient humans and animals have depressed thymic mass and increased susceptibility to hypogammaglobulinemia; (d) the sera of some individuals with hypogammaglobulinemia may contain residual antibodies which can, under certain circumstances, react with the infused gammaglobulin preparation.

In other investigations, lymphocyte activation in vitro following stimulation with a panel of mitogens, antigens, and allogeneic stimulator cells was assayed using freshly isolated peripheral blood mononuclear cells before and after the administration of both high protein and high carbohydrate diets. The data support the view that short-term dietary changes can influence the immune response.

d. Nutrition and Burns (A.C. Antonacci [NYH-CMC], S.E. Calvano [NYH-CMC], J.M. Davis [NYH-CMC], L.E. Reeves [NYH-CMC])

One of the objectives is to evaluate the effectiveness of parenteral nutrition on hypermetabolic burn patients and normal individuals. In addition, other preliminary studies are being pursued along the following lines: (a) T-cell subpopulations following thermal injury. A significant decrease in the number and percentage of total T-lymphocytes and T-helper cells was observed 24-48 hours postburn; (b) autologous and allogeneic mixed lymphocyte responses following thermal injury. We have demonstrated highly significant depression in autologous mixed lymphocyte responsiveness associated with concomitant suppression of normal T-cell radiated allogeneic MLR to burn non-T-cell stimulators; (c) defective natural killer and antibody-dependent cytotoxicity following thermal injury in man; (d) adherent cell production of prostaglandin E_2 following thermal injury in man; and (e) lymphocyte monoclonal antibody marker alterations following thermal injury in man.

e. Nutrition and Pharmacology (K.E. Anderson [RU], A. Kappas [RU], and J. Pinto [MSKCC])

The overall objectives are to determine (a) the effects of changes in dietary macronutrient composition on drug metabolism in normal subjects; (b) the effects of caloric restriction on drug metabolism in these subjects; (c) the metabolism of drugs in subjects fed highly purified diets and foods containing inducers or suspected inducers of the mixed function oxidases; (d) the role of aryl hydrocarbon hydroxylase (AHH) and other mixed function oxidases of gastrointestinal epithelium in neoplastic and inflammatory diseases in man; and (e) dietary effects on steroid hormone metabolism, as well as on lipid metabolism and immune function. A study on the effects of intake of charcoal broiled meat on the conjugation of acetaminophen was completed. Studies of the effects of administration of δ-aminolevulinic acid in vivo in laboratory animals have been published. An investigation on the effects of dietary fiber on hepatic and intestinal mixed function oxidations and on cholesterol synthesis in the rat has been published.

Other studies are designed to elucidate the hormonal, nutritional, and pharmacological variables which regulate vitamin metabolism, specifically riboflavin, to investigate the nutritional consequences of psychotropic drugs and alcohol on riboflavin metabolism, to provide new information on previously unrecognized hazards of usage of psychotropic drugs and/or ethanol in association with marginal or overtly riboflavin deficient diets and to examine the consequences of these effects in nutritionally vulnerable populations, e.g., the elderly and cancer patients.

f. Lipids (E.H. Ahrens, Jr. [RU], D.J. McNamara [RU], and N. Young [NYH-CMC])

The overall research program of these investigations is aimed at discovering the various pathogenetic mechanism leading to hyperlipidemia in the individual patient. This question has been approached by investigating the various parameters of cholesterol homeostatis in health and disease, and by developing and applying methods suitable for measuring these parameters in fairly large numbers of outpatients. In addition, studies investigating the therapeutic effectiveness of total parenteral nutrition and low density lipoprotein immunoadsorption in the treatment of cardiovascular disease are in progress. It is planned to continue investigations on the relationship between dietary fat quality and immunocompetence in man. These investigations also will determine the safety of proposed diets by use of the integrated studies approach available through the CNRU to determine the effect of dietary fat quality on lipid metabolism, drug metabolism, immunocompetence, prostaglandin metabolism, and other cellular metabolic systems.

Other related investigations are seeking to determine how insulin deficiency leads to hypercholesterolemia, and to evaluate the possibility that hyperphagia by diabetic rats affects cholesterol metabo-

lism and causes hypercholesterolemia. These studies will determine whether mechanisms for clearance of plasma lipoproteins are affected by insulin deficiency, and will determine the effects of diabetes on whole body cholesterol flux in rats eating chow ad libitum.

g. Nutrition and Brain (J. Blass [NYH-CMC], G.E. Gibson [NYH-CMC], J. Gibbs [NYH-CMC], and P.E. Stokes [NYH-CMC])

The overall objectives of these investigations are to (a) understand the effects of different nutritional states on brain biochemistry and function, centering around neurotransmitter and energy metabolism; (b) to establish the 2-deoxyglucose methods as a tool to study nutritional deficiencies, particularly niacin deficiency, in order to determine the pathophysiology of the dementias that accompany nutritional problems, and thereby to determine the effects of nutritional deficits on various brain regions.

Other investigations will seek to understand the peripheral and central physiological mechanisms controlling behavioral satiety for food, with particular focus on exploring the satiety actions of two brain-gut peptides, cholecystokinin (CCK), and bombesin (BBS), and to compare the pharmacokinetics of two stable lithium isotopes, Li-6 and Li-7, and to compare the behavioral, EEG, and potential toxic effects of these two isotopes, and to observe the effects of the isotopes on Na, K, and trace mineral contents of plasma and red blood cells.

University of Chicago CNRU

By

Irwin H. Rosenberg, M.D.

UNIVERSITY OF CHICAGO
CLINICAL NUTRITION RESEARCH UNIT

The overall objective of the University of Chicago Clinical Nutrition Research Unit (CNRU) is to facilitate and encourage clinical investigation on nutritional aspects of human disease. By extending the efforts of the Committee on Human Nutrition and Nutrition Biology, the CNRU will foster interdisciplinary efforts in research, patient care, education and training. A major goal is the application of current progress in laboratory and animal research to human nutrition investigation.

The University of Chicago CNRU consists of seven core laboratories, facilities for Nutritional Assessment and Support, and for Study Design and Data Management, and an administrative core that also coordinates education and training activities. The seven core laboratories include two for Lipids and Vitamin Assay, Trace Metal, Lipoprotein, Stable Isotope, and Radioassay Laboratories.

Ongoing research centers on lipid metabolism and cardiovascular disease, stable isotopes/breath tests, metabolism of vitamins, minerals and trace metals, and the interrelations of nutrition with growth, digestive disorders, and with diabetes. Patients being followed by the affiliated Nutrition Support Service are the focus of additional clinical protocols that draw on assays from several of the core laboratories.

Current goals include: 1) provide expanded access to existing facilities and services for nutrition research, 2) develop new analytical and research facilities, and 3) extend nutrition education, training and research activities.

Of the 16 new protocols that were initiated in 1982, nine involve investigators new to research in nutrition, in training, or new to the CNRU. Results of recent research conducted under the auspices of the CNRU are described briefly below.

EDUCATION AND TRAINING

These activities include the monthly research seminars of the Committee on Human Nutrition and Nutritional Biology, with special lectures by outside nutrition scientists, formal courses, special lectures in courses for medical and graduate students, clerkship/preceptorship opportunities for medical students and graduate students in clinical nutrition, the monthly Human Nutrition Journal Club, weekly Nutrition Support Service conferences, presentations at grand rounds and post-graduate courses by members of the Committee on Human Nutrition and Nutritional Biology, and presentations by the CNRU staff to community and other University groups.

As part of the enrichment program, Drs. Howard Hopps, Khursheed Jeejeebhoy, Howard Schutz, William Dietz, Rose Frisch, Mary Frances Picciano, Norman Kretchmer, George E. Bunce (et al.) presented seminars and met with students and CNRU staff. Norman Kretchmer presented the second Lydia J. Roberts Memorial lecture in May. This program, which is sponsored by the Quaker Oats Company, brings an outstanding nutrition scientist selected by the Committee on Human Nutrition and Nutritional Biology to Chicago. Dr. Kretchmer presented both a general interest

lecture on Nutrition and Evolution to the Chicago-area nutrition community and a research seminar at the University of Chicago, and additionally met with faculty, students, and CNRU staff. The monthly Human Nutrition Journal Club is beginning its third year, with participation extending to physicians in training, clinical dietetics, staff and graduate students.

Under the auspices of the CNRU, bimonthly Clinical Nutrition Research meetings have been instituted to serve as a forum for informing prospective investigators of new techniques available in the CNRU as well as to present preliminary data of general interest. These meetings have focused on either an area of research (e.g., calcium and vitamin D interrelationships) or the capabilities of one Core laboratory (e.g., stable isotope techniques for the determination of energy expenditure and breath tests using other stable isotopes) We are now establishing study groups in several areas of ongoing or potential research interest to enhance our focus on nutrition investigation. We anticipate that these groups will foster collaborative research efforts. Study groups now underway are addressing the nutritional physiology of body composition and clinical management and assessment of bone loss.

More formal educational activities include the master's program in clinical nutrition and a new Ph.D. program, which was established at the University in mid-1981 under the auspices of the Committee on Human Nutritional Biology. The number of applications for both programs have increased, with many received from medical students, residents and other physicians. In the Master's program, the curriculum has been expanded to include a research track in addition to the clinical track. Eight students are currently enrolled in the master's program, and three have matriculated in the new Ph.D. program.

Training activities include the Kraft Nutrition Fellowship program, which provides physicians-in-training the opportunity to emphasize nutrition in their research and studies. Four Kraft Nutrition fellows, two predoctoral, and two post-doctoral, have been appointed for 1982-83. New in 1982 is our first full-time Nutritional Fellow, whose training program will encompass several areas of internal medicine and pediatrics, as well as nutrition research.

STUDY DESIGN AND DATA MANAGEMENT

In this facility, an experienced biostatistician reviews all protocols submitted to the CNRU for study design considerations, and also consults with prospective investigators who are in the process of drawing up research protocols. Our computer specialist has developed several applications, particularly software. One package of programs enables the Nutrition Support Service to keep basic data on all patients seen, which allows retrospective review to find patients who meet certain criteria as well as pertinent patient information. Another program keeps detailed records on the progress of all patients followed in our home parenteral nutrition program. These programs were developed for a microcomputer system, and are extensively documented and transferable.

Nutrition research at the University of Chicago CNRU is described in the sections that follow.

VITAMIN METABOLISM

The Vitamin Assay Laboratory is set up to perform blood determinations of thiamin (transketolase-TPP effect), riboflavin (glutathione reductase-FAD effect), pyridoxine (EGOT-PLP effect), ascorbic acid, and vitamins A, D, 25-hydroxyvitamin D, and E.

New studies in the Vitamin Assay Laboratory include a survey of vitamin E levels and neuropathy in adult patients with cystic fibrosis and a survey of vitamin E and selenium levels in patients with chronic liver disease. One of the adults with cystic fibrosis who presented with neurological symptoms that others have attributed to vitamin E deficiency had no detectable tocopherol in the serum despite oral supplementation. After intramuscular administration of vitamin E, her neurologists noted evidence of improvement that was associated with detectable, although still low, serum vitamin E. Nine such patients are being followed; basic studies of vitamin E absorption have begun as a result of these findings. A study of folic acid absorption in patients on and off cimetidine is continuing, as are studies of other drugs and folate absorption and of intestinal hydrolysis and absorption of other B vitamins. Concentrations of folate and folate binding protein in human milk were found to be positively correlated in another study conducted in this laboratory. Ongoing clinical and experimental studies of vitamin D absorption and metabolism and of vitamin D status and calcium absorption in gastrointestinal disease are continuing.

STABLE ISOTOPES AND BREATH TESTS

The Stable Isotopes Laboratory is pursuing 12 projects in collaboration with 10 investigators, three of whom are new to the CNRU. The protocols include studies of fatty acid oxidation in children with Reyes syndrome, oxidation of lactic acid in man during exercise, and fat absorption in a patient with abetalipoproteinemia. Other projects have continued, including a study to validate anthropometric measurements for estimating lean body mass in obese adolescents against total body water determinations. Total body water is also being measured in institutionalized children and in children with cerebral palsy and myelodysplasia.

The validation of the doubly-labeled water method for determination of energy expenditure has continued, with extremely promising results from the four subjects for whom analyses are complete. Another four subjects have been studied. Studies to characterize the carbon isotope composition of the human food chain have continued.

Studies of the aminopyrine breath test for assessing hepatic cytochrome P-450 activity and the caffeine breath test for assessing cytochrome P1-450 have continued. In addition, the phenacetin breath test is being evaluated as a possible measure of hepatic blood flow. All of these tests involve measurement of $^{13}CO_2$ excretion in the breath as an index of hepatic metabolism.

LIPID METABOLISM AND CARDIOVASCULAR DISEASE

The Lipids Laboratory has provided measurements of serum triglyceride, cholesterol, cholesterol esters, free fatty acids, serum phospholipids,

and lipoprotein electrophoresis for several ongoing and new investigations. Continuing in vitro studies indicate the complexity of the apoprotein exchanges that occur between human HDL and Intralipid particles, which may be of physiologic significance.

Lipoprotein-apoprotein and lipid profiles are being measured prospectively in free-living insulin-dependent diabetics as part of a multicenter clinical trial to assess the effects of improved blood sugar control on metabolic and microvascular parameters. A biobehavioral study to assess the role of lipid factors present in maternal rat feces in fat absorption and cerebral development of neonatal rats is in progress. The Lipids Laboratory is also measuring lipid metabolic parameters in a study of the effects of estrogen replacement therapy in post-menopausal women. In another new study, the effect of parenteral therapy with dextrose alone on surfactant fatty acid concentrations is being examined to determine whether essential fatty acid deficiency might result in patients held on this therapy during assisted respiration.

Research has continued in Lipids Laboratory II on the oxygenated sterol compounds, which are potent inhibitors of sterol synthesis in a variety of mammalian cells in tissue culture. Recent findings indicate that all density classes of human serum lipoproteins bind oxygenated sterol compounds, and that lipoproteins can act as acceptors of oxygenated sterols previously inserted into red cells. Human low-density lipoproteins compete more effectively than high-density lipoproteins with red cell membranes for oxygenated serum compounds. When long-term human B-lymphocyte lines were used as a model of nucleated mammalian cells, results paralleled those for insertion of oxygenated sterol compounds in red cell membranes. Several studies of cholesterol synthesis in leukemia cell lines are described in detail in the technical progress report that follows.

In the Lipoprotein Laboratory, in vitro studies of the interaction between Intralipid and lipoproteins have continued. Recent results indicate that the in vivo exchange of apoproteins between chylomicrons and high density lipoproteins may be affected by the physical properties of the apoproteins, rather than the action of lipolytic enzymes. The work has also led to the successful isolation of apoprotein A-IV from human plasma in amounts sufficient for characterization of its physical properties as well as electroimmnunoassay studies of its concentration in patients with a variety of lipoprotein disorders. Also in this laboratory, a method has been developed for the rapid fractionation of the major apoproteins of plasma lipoproteins. The apoproteins are isolated in highly pure form with good yield in about 30 minutes using high-performance liquid chromatography.

In collaboration with Litton Bionetics (Kensington, MD), the Lipoprotein Laboratory has screened about 100 rhesus monkeys to assess the relationship between genetic and dietary factors in the expression of hyperlipidemia caused by administration of a high-fat diet containing 15% fat and variable amounts of cholesterol. One of the goals of this project is to establish the molecular basis for the "low responders," the animals that show no change in lipoprotein and cholesterol profiles in spite of their high fat intake.

Another study involves the use of oral Intralipid for studying the relationship between cholymicrons in lymph and plasma of normal and hyperlipidemic dogs. This study addresses the nature of the processing of cholymicron apoproteins, particularly apo A-I and apo A-IV, during their transfer from lymph to plasma.

DIABETES AND NUTRITION

Studies conducted in the Radioimmunoassay Laboratory indicate that the insulin resistance associated with cirrhosis may result in part from decreased binding of insulin to target tissues, as insulin binding by erythrocytes and monocytes was significantly decreased, probably because of a decreased receptor number per cell that is not related to basal insulin levels. Surface receptors for pancreatic hormones in dog and rat hepatocytes were found in another study to be associated with differences in qualitative and quantitative aspects of hormone-target cell interactions.

Another protocol assessed the risk and possible mechanisms of hypoglycemia occurring during moderate exercise in insulin-dependent diabetics receiving a constant insulin infusion. Under the conditions used, exercise did not result in hypoglycemia. A study of rat and dog plasma indicated that somastostatin is present and that it may be a hormone distinct from SRIF. In an experiment with dogs, glucose ingestion was shown to rapidly increase the extraction of insulin by the liver, which was associated with decreased hepatic glucose output.

NUTRITION AND GROWTH

Studies of the mechanism by which chronic intestinal diseases alter nutritional status and linear growth are continuing. About 60 children with chronic inflammatory bowel disease are being followed longitudinally to correlate changes in nutrient intake, measures of nutritional status, and specific hormone levels (including the somatomedins) with growth velocity.

Somatomedin concentrations increase with (and usually preceding) improved growth velocity. Quantitation of enteric protein loss has recently been added to this study. Recent results indicate that genetic factors may be more important in influencing the incidence of lactose malabsorption in these patients than the degree of intestinal disease. Analyses are in progress for the first patient in a protocol to study energy expenditure/balance in children with Crohn's disease during nutritional support. A multi-center study of 13C-labeled lipids in the assessment of gastrointestinal and pancreatic disease, also conducted in collaboration with the Stable Isotopes Laboratory, has been completed.

TRACE METAL METABOLISM

Renovations for this laboratory are near completion. It has been designed and equipped to do the greatest range of trace elements possible with accuracy and precision in a variety of biological tissues. When operational, this laboratory will have unique capabilities for research in a clinical setting. The investigators are using an instrument located in another department at the University of Chicago to pursue two interim

projects, one on zinc status and immune function, and the other on zinc, copper, and iron interactions in mammalian species. Studies of cell lines and other tissues that might provide a clinically useful indicator of trace metal status are planned for the new laboratory. Sampling to establish normal ranges of several trace elements for the laboratory has begun.

NUTRITION SUPPORT SERVICE

The Nutrition Support Service is involved in several clinical research protocols. Two studies concern the mechanism of the hypercalciuria often observed with TPN. One is assessing the effect of protein intake while the other concerns the effect of infusion rate (continuous vs. intermittent infusion schedule) on calcium excretion. Correlative experimental studies are also in progress, and both protocols include insulin assays provided by the Radioimmunoassay Laboratory.

A prospective study of the changes in serum lipids and lipoproteins that occur during parenteral nutrition is underway; under the auspices of Lipids Laboratory I, changes in serum triglycerides, cholesterol, free fatty acids, phospholipids, and HDL-cholesterol are being documented in these patients. Another ongoing study compares the efficacy of semipermeable and occlusive dressings in preventing catheter-related infections; 19 patients have been studied to date.

In another study, the stability of thiamin in parenteral solutions containing sulfite ions as a preservative was examined. Thiamin was found to be stable in typical TPN solutions containing amino acids, dextrose, multivitamins, etc. However, when multivitamins with thiamin were added directly to amino acid solutions containing 0.1% sulfite, significant degradation (60% in 22 hr) occurred.

A pilot protocol addressing the mechanism of hypouricemia associated with total parenteral nutrition was recently initiated in collaboration with nephrologists from Michael Reese Hospital. The purpose of the study is to determine whether uricosuria accounts for the significant hypouricemia observed and also to define the time course of this phenomonon. Additional studies are planned.

SUMMARY

With the designation of the University of Chicago Clinical Nutrition Research Unit, many diverse research, education, and clinical activities in nutrition have been enhanced. The network of core laboratories has facilitated interdisciplinary approaches to research on nutritional aspects of human disease, while enabling ongoing basic research to continue. These facilities have also increased diagnostic capabilities and fostered the increasing activity of the Nutrition Support Service in patient care and consultation. The CNRU has, by building on the expertise of existing research programs, stimulated nutrition research activity at the University of Chicago. Educational efforts have been increased in response to growing interest and awareness.

University of Wisconsin CNRU

By

Earl Shrago, M.D.

CLINICAL NUTRITION RESEARCH UNIT
UNIVERSITY OF WISCONSIN - MADISON

Co-Principal Investigators: Earl Shrago, M.D. - Alfred E. Harper, Ph.D.

OVERVIEW OF ONGOING ACTIVITIES

The Clinical Nutrition Research Unit (CNRU) at the University of Wisconsin is actively engaged in the support of research, education and training, and patient care in the area of clinical nutrition. The faculty and staff include physicians and Ph.D. scientists from a variety of departments in the Medical School, University Hospitals and the College of Agricultural and Life Sciences. This environment has afforded us the opportunity of carrying out our primary mission, mainly to serve as the focal point for the pursuit of fundamental research in clinical nutrition.

The CNRU, therefore, supports a broad area of research in clinical nutrition cutting across the boundaries of basic and clinical science which reflects the diversity of interests of scientists at the University of Wisconsin and takes advantage of unique opportunities offered by various programs on the campus such as the Cancer Center and Specialized Center of Research in Metabolism and Nutrition of Infant Lung Disease. The major areas of research emphasized in the CNRU are: carnitine nurtriture and its potential deficiency in disease states and carnitine therapy; the effects of nutrients and natural products on serum lipids, particularly total and HDL cholesterol; and the adverse effects of total parenteral nutrition leading to complications of fatty liver and metabolic bone disease.

The research projects are an integral part of our training program. In addition to postdoctoral fellows and graduate students working in the laboratories of the individual investigators associated with the CNRU, the University supports four M.D. fellowships in clinical nutrition. All of the fellows participate in some related research project and maintain continuous involvement with the Nutritional Consultation and Support Service in the hospital and clinics. Future plans call for the initiation of a predoctoral and postdoctoral training program in oncology and nutrition involving both the clinical and basic science faculty with special emphasis being given to an M.D. - Ph.D. program in clinical nutrition.

Within a relatively short time span the impact of the CNRU on a Campus with a long tradition of research in experimental nutrition has been quite impressive. In particular, the integration of clinical nutrition into Medical School education, patient care in the hospital and clinics and cooperative research projects with faculty in the clinical departments has been very successful and is gaining in momentum.

DESCRIPTION OF ONGOING RESEARCH

A multidisciplinary group of scientists in the Clinical Nutrition Center including biochemists, exercise physiologists, nephrologists, as well as nutritional scientists have been studying the metabolic and clinical consequences of a carnitine deficiency state brought about by dialysis therapy. The patients, almost all of whom had a Type IV hyperlipoproteinemia, have been subjected to prolonged hemo or peritoneal dialysis. During dialysis therapy, an acute precipitous decrease in serum carnitine was observed with an equivalent rise in concentration in the dialysate. In some patients subjected to muscle biopsy, a 50% decline in free and total carnitine was also detected, and this was not influenced by a prolonged period of exercise. The patients' diets were analyzed for carnitine and found to be adequate in terms of intake, however, synthesis of carnitine by the kidney might be compromised.

Future studies are being directed toward investigation of the potential significant inverse relationship between serum carnitine and VLDL concentration. Moreover, protocols are being prepared to study the effect of L-carnitine supplementation on concentrations of serum VLDL, LDL and HDL in normal volunteer subjects on various dietary regimens and in patients with Type IV hyperlipoproteinemia associated with low HDL levels. Since serum carnitine values do not accurately reflect tissue concentrations, and muscle biopsy is not appropriate for routine use, a method to determine the concentration of carnitine in platelets is being developed. This cellular source, which is accessible and is known to concentrate carnitine, may well reflect the overall tissue concentrations.

A comprehensive investigation is being carried out on the effects of various nutrients and natural products on total and HDL cholesterol. A major study was possible in one particular area as the Department of Human Oncology at the University is one of the major centers for interferon therapy. Following up a letter to the editor in a leading medical journal indicating that α-leukocyte interferon decreased HDL levels in three volunteer subjects, a major study has been underway in which not only α-leukocyte interferon which is only 20% pure, but also the pure recombinant DNA interferon and β-fibroblast interferon were tested in a large group of well controlled patients whose dietary history was also obtained. Both total cholesterol and HDL cholesterol fell during therapy with α-leukocyte and recombinant DNA interferon and returned to normal following cessation of therapy. In a second study which has not involved a large enough group of subjects to obtain statistically significant numbers, there appears to be a somewhat different effect with fibroblast interferon in that total cholesterol drops, whereas, the HDL levels remain approximately the same, implying that the change occurred in the LDL fraction. These investigations are being intensively pursued.

An epidemiologic and clinical study is being carried out on the link between anemia, particularly that due to iron deficiency, and serum cholesterol which appears to stand up after the general nutritional status

of the subject has been taken into consideration. A significant positive correlation between hematocrit and serum cholesterol levels in both patients and healthy subjects after taking age, sex, body weight and height into account has been observed. Similar studies are underway on sporadic and frequent blood donors. Also, a study is being done to determine whether the serum cholesterol and HDL levels in patients who have hereditary spherocytosis are significantly different from those of their siblings who do not have anemia. Finally, an animal model, the sex-linked, iron-deficient anemic mouse, is being tested to determine the mechanism for the relationship between hematocrit and cholesterol.

As part of a large project on the effect of trace metals on human mineral metabolism, a study of effects of ingestion of small amounts of aluminum on blood lipid levels and vitamin D metabolism was carried out on human volunteers. Following aluminum ingestion, serum levels of 25-hydroxy vitamin D were lower although they were not significantly lower during the treatment. Dietary aluminum intake did not affect serum lipid levels. Under the supervision of recognized experts on the faculty of the Department of Nutritional Sciences, the Core Laboratory of the CNRU has taken responsibility for selenium analyses which will be performed on request for other Centers around the country.

A concerted effort is being made to elucidate and understand the factors leading to certain complications from total parenteral nutrition. In particular, the development of fatty livers following infusion of nutrients is being studied in the rat maintained on continuous intravenous feeding. As serum enzyme changes used to detect fatty liver are poor indicators of early fat infiltration, particular emphasis is being placed on methodology to detect fatty infiltration by the use of lipophilic radiopharmaceuticals administered to the patient so that hepatic retention can be quantitatively determined by external measurements. These latter studies are being carried out in collaboration with the Nuclear Medicine Section in the Department of Radiology, and the project will soon be implemented in human subjects.

An in-depth nutritional assessment study on patients with chronic obstructive pulmonary disease was carried out with the collaboration of the members of the Pulmonary Division of the Department of Medicine. The patients who come from all over the State of Wisconsin are part of a rehabilitation program to determine the most efficacious therapy for their chronic lung disease. It was found that in a number of cases which made up a selective sub-group, nutritional supplementation proved to be of therapeutic value. Studies are now going on to determine the mechanism for the hypercatabolic state in many of these patients as well as the relationship of nutrition and exercise, particularly movement of the intercostal muscles, to the elevated levels of serum high density lipoprotein cholesterol which has been recently detected. In related clinical studies, research support in the form of laboratory technology and nutritional assessment is also being given to a project on the

epidemiology of retinopathy in diabetes and to a study of the effects of a number of nutritional variables in a group of patients with anorexia nervosa.

In a recently completed project a faculty investigator and research fellow in the Clinical Nutrition Center participated in a very important study providing definitive information that the α amylase inhibitor formulation (starch blocker) is ineffective in Man (Science 28 January 1983, pp. 393-394). The critical data in man was obtained with the breath hydrogen analyzer, an item of equipment belonging to the Core Laboratory of the Clinical Nutrition Center. This study also permitted the development of breath hydrogen analyses for clinical use, and the test is now part of the diagnostic armamentarium of the Nutrition Consultation Service in the hospital.

Columbia University CNRU

By

Myron Winick, M.D.

SUMMARY OF CNRU ACTIVITIES

Columbia University College of Physicians and Surgeons

The CNRU at Columbia University College of Physicians and Surgeons consists of 3 core components: Clinical, Laboratory, and Biomathematics. In addition, the CNRU supports a New Investigator as well as a number of pilot projects. The clinical and research activities of the unit are channeled through these components. Educational activities include the academic and public education programs of the Institute of Human Nutrition headed by Dr. Myron Winick, also Director of the CNRU, as well as the clinical teaching activities of all members of the CNRU staff.

The clinical core, directed by Dr. William C. Heird, includes a team of physicians, nutritionists, nurses, and technicians. The nucleus of this team is the Nutrition Support Service of Babies Hospital (Presbyterian Hospital in the City of New York); additional personnel to assure availability of all nutritional support activities for research as well as clinical needs are supported by CNRU funds. Unique components available only for research needs include availability of neuro-psychological follow-up and studies of energy expenditure.

The Laboratory Core component, headed by Dr. Ralph B. Dell, includes an amino acid laboratory, a lipid laboratory, and a general biochemistry and nutrition laboratory. The assays performed by these laboratories are available to any investigator within the University provided the study of which they are a part meets the approval of one of the CNRU's advisory committees. Unlike the Clinical Core, this component is available for research purposes only.

The Biomathematics Core component, directed by Dr. Rajasekhar Ramskrishnan, includes biostatisticians and computer programmers. This team is available to help with study design as well as data analysis. The facilities of the group are shared by other major research activities, one directed by Dr. William C. Heird, Department of Pediatrics (Nutritional Goals vs. Tolerance in LBW Infants), and another directed by Dr. DeWitt Goodman (Atherosclerosis SCDR), Department of Medicine. The group also has close ties to the CLINFO system of the General Clinical Research Center.

The academic program of the Institute of Nutrition includes both Masters and Ph.D. degree programs, a required course for second year medical students and a general lecture series for the entire institution. Public educational activities include a yearly symposium, a monthly newsletter, and a public radio program.

Major general areas of research supported entirely or in part by the CNRU are directed toward nutrition of low birth weight infants, metabolic effects of total parenteral nutrition, cholesterol turnover and metabolic response of stressed patients. While research in all these areas continues, a number of specific studies have been completed.

A specific study related to the general area of low birth weight infant nutrition has established that taurine supplementation of infant formulas maintains body taurine pools but does not affect intestinal fat absorption, as would be expected if maintenance of taurine pools increases bile salt pool size. Another study in this general area has shown that plasma and urinary cyst(e)ine concentrations are similar in low birth weight infants fed formulas containing unmodified cow milk protein (which contains very little cysteine) or modified cow milk protein (which contains twice as much cysteine). This latter study also established that the metabolic acidosis observed in low birth weight infants fed unmodified cow milk protein formulas but not in infants fed modified cow milk protein formulas results from accumulation of nonmetabolizable or unmetabolized organic acids. These, in turn, are produced from excess amino acids.

A study exploring the hypothesis that improving the nutritional status of patients with cystic fibrosis (with short-term total parenteral nutrition) will improve pulmonary function has been completed. Results show improvement of respiratory muscle strength during the period of total parenteral nutrition; however, oxygen saturation decreases during this time, probably as a result of fluid accumulation during total parenteral nutrition. Future studies in this area will confirm this latter assumption and also explore the hypothesis that maintenance of improved nutritional status (with long-term parenteral nutrition) will result in maintenance of, and perhaps continued improvement in respiratory muscle strength.

Studies to define the requirements of amino acids for parenteral nutrition, begun a number of years ago, have continued with CNRU support. These studies have resulted in formulation of a mixture of amino acids that appears to produce normal plasma concentrations of all amino acids in infants and young children requiring total parenteral nutrition. Studies are planned in animals to determine if parenteral nutrition regimens that result in normal plasma and tissue amino acids patterns are beneficial with respect to ongoing protein synthesis.

Additional studies in patients requiring total parenteral nutrition suggest that the ratio of linoleic and linolenic acids in parenteral lipid emulsions is of considerably greater importance than in dietary lipid. When administered parenterally, even a modest amount of linolenic acid appears to inhibit conversion of linoleic acid to arachidonic acid. On the other hand, parenteral lipid emulsions that contain no linolenic acid result in a low content of linolenic acid and metabolites within plasma phospholipids. Future studies in this area will define the optimal amounts of both linoleic and linolenic acid required to maintain a "normal" fatty acid pattern of serum and tissue lipids. Other studies in this area will determine the effect of abnormal plasma lipid fatty acid patterns (e.g., low content of arachidonic acid) on prostaglandin production.

National Institutes of Health

Intramural Program in Nutrition Research

by

Artemis P. Simopoulos, M.D.

NATIONAL INSTITUTES OF HEALTH
INTRAMURAL PROGRAM IN NUTRITION RESEARCH

Institutes supporting intramural research in nutrition include NCI, NHLBI, NIDR, NIADDK, NIAID, NICHD, NEI, NIEHS, and NIA. Most of this research takes place on the NIH campus in Bethesda; however, the NIEHS staff conducts research in Research Triangle Park, North Carolina, and the NIA intramural program is located at the Gerontology Research Center in Baltimore, Maryland.

Intramural research projects include prospective randomized clinical trials, longitudinal studies on the metabolism of nutrients and on food toxicity in healthy volunteers and patients with various disease states, and animal studies. Among the ongoing long-term studies are: the U.S. cancer mortality survey, in which the role of nutrients in cancer mortality is an important component; studies on the effects of total parenteral nutrition in cancer treatment; the Type II coronary intervention study, which seeks to determine whether lowering LDL cholesterol will slow, stop, and/or reverse the progression of coronary artery disease in patients with hypercholesterolemia; and longitudinal studies on human aging.

The bulk of the NCI intramural research lies within the general category of skin cancer chemoprevention through the use of vitamin A. Several researchers are analyzing the morphological effects, biochemical mechanisms, metabolic pathways, and dose toxicity of synthetic vitamin A (13-cis-retinoic acid) and its analogues in cell cultures and laboratory animals.

These studies should provide information on the cellular and molecular basis of skin carcinogenesis as well as the therapeutic value and anti-promoting properties of vitamin A, before and after the onset of malignancy.

NCI has several research projects evaluating the relationship between nutrition and cancer etiology. Cross-cultural surveys and case control studies are under way to study the incidence of bladder, breast, colon, and other cancers in regard to dietary patterns among target groups. These projects are attempting to isolate nutritive factors in cancer etiology from other variations in lifestyle among the study groups. A NCI study is looking into the carcinogenicity of foodstuff contaminants and artificial sweeteners in primates. The effects of specific fatty acids and lipotropes in modifying the uptake and resistance to carcinogens in mammary and liver cells and the impact of manipulation of hormones and dietary lipid intake on mammary tumor incidence are being evaluated.

Basic research in energy exchange and expenditure, conducted on experimental animals, involves the use of whole body calorimetry to investigate differences between normal and tumor bearing animals. In addition, these experimental studies should elucidate the physiological basis of cachexia, which often characterizes cancer patients.

NCI is actively involved in assessing the efficacy of TPN as a means of nutritional support for the cancer-bearing host. Prospective randomized protocols for the use of TPN as an adjunct to aggressive chemotherapy and radiation treatment are under way. In addition, the NCI intramural program operates a large service component in which patients receiving TPN at NIH are studied for deficiencies in vitamins, trace metals (zinc, copper, chromium), essential fatty acids, and efficacy of TPN. Studies are done on gluconeogenesis, protein synthesis, glucose disposal, body composition of potassium, alanine kinetics, mineral balance, and requirements for all known nutrients.

Scientists in NHLBI are working toward delineation of the molecular and structural properties of the human plasma apolipoproteins, the physiological role of the apolipoproteins and lipoproteins in lipid transport, the determination of the mechanisms involved in regulation of cellular cholesterol metabolism and transport, and the elucidation of the metabolic and molecular mechanisms involved in plasma lipoprotein biosynthesis, transport, and catabolism in normal individuals and patients with disorders of lipid metabolism and atherosclerosis. Other research is exploring iron chelation in transfusional hemosiderosis, hematopoiesis in bone marrow failure, biochemistry of the spontaneously hypertensive rat, regulation of tyrosine hydroxylase in the central nervous system, and metabolism of lipids in human fibroblasts and muscle cells grown in culture.

Intramural research at NIDR includes studies on taste and cariogenicity of foods and their relationship to the food or nutrient intake of infants and adults.

NIADDK conducts nutritional studies directed toward (1) determining the nutritional, biochemical, and metabolic roles of a variety of nutrients considered to be essential in the diet and (2) measuring the effects of different levels of nutrient intake on tissue levels of various metabolites in laboratory animals. These studies relate to dietary measurements, nutrient bioavailability, nutrient interactions, nutrient status, and metabolic function. Special emphasis is being given to vitamins A and E, folacin, and zinc.

Intramural clinical research is also conducted on nutritional factors that relate to etiology, morbidity, and mortality of metabolic and other diseases. Of special significance are studies on (1) bone metabolism and osteoporosis; (2) pathogenesis of human cystinosis; (3) effects of weight reduction on glucose tolerance and glucoregulatory hormones; (4) followup on infants fed infant formula deficient in chloride; (5) malabsorption, fatty acids, and membrane function in cystic fibrosis; and (6) lipoprotein composition in Indians and Caucasians. Other studies include traumatic shock and cellular immunity, mechanism of action of pyridoxal phosphate, hepatic and intestinal function, role of dietary fat in regulating adipose cell function, $(NA^{+} + K^{+})$ ATPase activity in obese subjects, and transport of lipids, hormones, and enzymes.

An NIAID researcher is investigating the mechanisms of food allergy, focusing on the mechanisms of basophile and mast cell histamine and

leukotriene release in the bowel, and ways in which food substances trigger that release. Histamine and leukotrienes are the pharmacological substances in the body which produce the tissue reactions recognized clinically as being allergic. Thus, they may be responsible in part for the gastrointestinal upset, rashes, and other signs and symptoms of food allergies.

Numerous intramural nutrition research projects are carried out by NICHD. Scientists are studying the way in which a cell coordinates the expression of its genetic repertoire under conditions of nutritional deficiency, the electro-physiological effects of long chain free fatty acids on spinal cord cells in tissue culture, and trends in breast and bottle feeding among Pima women of the Gila River Reservation in Arizona. Researchers are also working to improve the therapy of severe hypoglycemia and the nutritional therapy of glycogen storage diseases; in collaboration with scientists from the National Institute of Mental Health, NICHD researchers have established a protocol to study the effects of sugar on hyperactivity in children whose parents have observed that dietary sugar incites hyperkinetic behavior.

In other NICHD research, scientists are working to develop new stable isotope probes to study human calcium metabolism in lactation and in various metabolic disorders, such as dystrophic calcification. In attempts to better understand the phenomenon whereby changes in nutritional environment during development and growth modify differentiation and maturation of cellular processes, researchers are continuing their investigations of nutritional modulation of genetic expression in the developing mammalian pancreas. Research is continuing, too, on various inborn errors of metabolism, including glutathione synthase deficiency, glucose-6-phosphate dehydrogenase deficiency, cystinosis, homocystinuria, phenylketonuria, adrenal leukodystrophy, and galactosemia; various kinds of experimental nutritional therapies are being investigated in these disorders. Investigators are also attempting to ascertain if vitamin E administration will reduce neonatal hyperbilirubinemia secondary to glucose-6-phosphate dehydrogenase (G6PD) deficiency, and whether vitamin E administration will reduce the frequency and severity of the acute hemolytic crises responsible for the major morbidity and mortality in this prevalent genetic disease. The effects of beta-carotene, another antioxidant, in chronic severe G6PD deficiency are also being examined.

Studies involving vitamin A (retinol) play a major role in NEI intramural research. Although the special role that vitamin A plays in vision is well known, the more general role this vitamin and its derivatives play in differentiation and maintenance of ocular epithelial tissues is less well understood. NEI scientists have developed preliminary biochemical data which shows that a normal metabolite of retinol, retinoic acid, has a specific cell receptor on both normal retina and retinoblastoma cell nuclei in culture. This may provide important additional information on the role of retinol in vision and the role of its derivative retinoic acid in the maturation and maintenance of epithelial cells.

Other NEI intramural investigators are studying the interrelationships of vitamins E and A in maintaining structural components of the retina in four groups of weanling rats fed purified diets adequate or deficient in each vitamin. In the normal retina, lipofuscin deposits build up as organisms age. Results from this study to date have indicated that when vitamins A and E were present in sufficient quantities, the lipofuscin granules did no accumulate; however, there was an accumulation when either or both vitamins were deficient in the diet.

The corneas of retinol deficient rats maintained on low levels of retinoic acid in a conventional laboratory environment, and corneas from retinol deficient rats receiving no retinoic acid or retinoic acid for 5 weeks and kept in a germ-free environment, were examined for structural abnormalities before the onset of apparent xerophthalamia. All groups of deficient rats showed abnormally large numbers of exfoliating cells, increased density of keratofibrils throughout the epithelial layer, decreased glycogen content, deposits of electron dense particles in the basal lamina region, and accumulation of electron dense bodies in the keratocytes. These changes probably occurred as a primary effect of vitamin A deficiency. However, the absence of neovascularization and inflammation of the corneal stroma in the germ-free rats suggest that these changes may be secondary, perhaps due to infection.

The intramural nutrition research of NIEHS focuses on development of approaches to study the regulation of gastrointestinal functions. Of particular concern are regulation of intestinal absorption and metabolism, and responses related to oral exposure to toxins. Current examples of these studies are the role of L-glycerol-3-phosphate in colon energy metabolism, NAD linked L-glycerol-3-phosphate dehydrogenase in the metabolism of methylazoxymethanol and tumorogenesis, factors involved in relative rates of intestinal tip and crypt cell protein synthesis by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). The regulation of these processes is examined at the cellular, subcellular, and molecular levels.

NIA intramural scientists are studying several aspects of nutrients as they relate to the aging process or the aged. A major area of interest is the mechanism(s) by which undernutrition increases life span. One hypothesis under study is that dietary restriction increases life span by reducing the use of the genetic code and thus minimizing genetic imperfections which may accumulate in later life. Two invertebrate model systems have been established for this purpose. Another study involves the effects of nutritional restriction on the age-related loss of dopamine receptors.

An important aspect of the NIA intramural program involves human studies relating aging, nutrition, and energy metabolism; studies, for example, on the secretion and action of gastric inhibitory polypeptide, on the relation between body weight and morbidity and mortality, and on the effect of dietary chromium on tissue sensitivity to insulin. Techniques for accurate measurement of serum and

urine levels of chromium have recently been developed, and are being used in a study to establish age and sex adjusted normal serum levels. Chromium has also been postulated to influence the development of coronary heart disease through its effect on lipid metabolism. This study will examine fasting chromium levels in individuals with and without coronary heart disease, and serum lipid levels prior to and following chromium supplementation.

Reports in the literature suggest that the rate of secretion and/or the composition of saliva are altered with increasing age. These findings are being re-evaluated as part of an assessment of the oral physiological status of a subset of participants in the Baltimore Longitudinal Study of human aging (BLSA). Work has been concentrated on (a) general demographic and dental descriptions of the participants, (b) evaluation of fluid output and exocrine protein secretion from stimulated parotid salivary glands, and (c) evaluation of taste acuity and taste intensity perception. Generalized age-related changes in salivary gland function were not found in this group of subjects, although specific age-related changes in electrolyte handling were noted. In a related study, age related changes in salivary gland function are being studied using both parotid and submandibular glands from young and aged rats; these studies have so far focused on the mechanism of protein synthesis and release, and on the control of gland function by neurotransmitters.

NIA intramural scientists, in collaboration with scientists at the USDA-Tufts University Center for Human Nutrition and Aging, have begun plans for a retrospective analysis of dietary data collected from participants in the BLSA. Participants during the years 1961 to 1965 and from 1968 to 1975 completed 7-day dietary diaries preceding each visit to the Gerontology Research Center. These visits are scheduled at 1- to 2-year intervals depending on the age of the subject. Nearly 200 participants completed at least one such diary in each of the three 5-year intervals 1960-65, 1966-70, and 1971-75. The planned analysis will involve assessment of daily variability of nutrient intake as well as variability from one visit to the next for individual participants.

Supporting all the Institutes in their intramural research is the Division of Research Services (DRS). The DRS laboratory animal nutrition research program works to improve the quality of laboratory animals being produced for research by improving their nutritional status. Series of feeding trials are designed to evaluate new diets and to determine the nutrient requirements of various strains or stocks of animals within a species. Data obtained from these studies form the basis for formulating diets having optimal nutrient concentrations for specific animals. These data are used to develop standard reference diets for use throughout NIH and the entire biomedical research community. Diets with either deficient or excess nutrient concentrations are evaluated to provide animal models with nutrition related diseases for study by NIH investigators. Studies are also conducted to develop satisfactory diets for the various animal species being introduced to biomedical research as new models.

The intramural nutrition research program of NIH complements and augments the extramural program by concentrating on research particularly relevant to the mission of the Institutes that utilize the facilities and scientific expertise available on the NIH campus.

Food and Drug Administration

Overview of Program -- Management and Scientific Emphasis

By

Allan L. Forbes, M.D.

OVERVIEW OF FDA PROGRAM -- MANAGEMENT AND SCIENTIFIC EMPHASIS

FIRST ANNUAL CONFERENCE

OF

FEDERALLY SUPPORTED HUMAN NUTRITION RESEARCH UNITS

NATION ACADEMY OF SCIENCES

DECEMBER 16-17, 1982

BY: ALLAN L. FORBES, M.D.
ASSOCIATE DIRECTOR FOR NUTRITION
AND FOOD SCIENCES
BUREAU OF FOODS, FDA

We are very pleased indeed to participate in this First Annual Conference. It seems to me that the idea of annual conferences at the Federal level on our favorite subject of nutrition research is long overdue. Personally, I think it is the best thing the OSTP Joint Subcommittee on Human Nutrition Research has come up with to date, and we look forward to participating in this type of activity in the years ahead. It's great to find out firsthand what the other agencies are doing.

The FDA Nutrition Research Laboratories were established in 1938, so we have been in business for almost 45 years. Today the FDA budget for nutritional activities approximates $8.7 million annually, involving over 175 personnel. About half of both dollars and people are devoted to research. Most of FDA's nutrition work is performed in-house, our extramural budget for contract research having decreased to less than $1 million this fiscal year.

The earliest work -- which continues to this day -- is in the area of development of chemical, microbiological and animal methodology to analyze the nutrient composition of foods. Perhaps one of the best examples is the work of Elmer M. Nelson and coworkers who, in 1938, developed that rat bioassay determination of vitamin D in milk as an urgently needed method to measure compliance with one of the first standards promulgated under the brand new Food, Drug and Cosmetic Act, i.e., for vitamin D milk. Although new methods using high pressure liquid chromotography are now available, the Nelson bioassay remains to this day as the standard method to determine the vitamin D content of foods.

Since the 1940's, FDA scientists have been working in the field of nutrient bioavailability, first on vitamins and, more recently, on minerals. In 1977, for example, James C. Fritz and coworkers published the rat hemoglobin repletion test for measuring iron

bioavailability -- a method now accepted by the Association of Official Analytical Chemists as the best method for such bioavailability measurement.

Another example of an historical contribution is the work of O.L. Kline and coworkers who published their work in 1942 on a convulsive syndrome in young rats associated with vitamin B_6 deficiency. This basic observation led to immediate identification of the etiology of the convulsive disorder observed in late 1952 and early 1953 in infants fed a specific infant formula which proved to be B_6 deficient because of excess thermal processing. As many of you will recall, after many years with FDA as Director of the Division of Nutrition, Dr. Kline retired several years ago as Executive Officer of the American Institute of Nutrition.

Some of the earliest clinical work on chromium effects on glucose tolerance was conducted by L.L. Hopkins of our laboratory in the mid-60's. Over the last decade, Dr. Mattie Rae Fox has developed the Japanese quail as an outstanding model for the study of nutrient deficiency, imbalance and toxicity and for measurement of bioavailability of minerals in foods, the number of papers in peer-reviewed journals now numbering approximately 30. Dr. Fox was also the first investigator to demonstrate the protective effect of ascorbic acid on cadmium intoxication. In recent years, we have focused on nutritonal relationships to heavy metals. For example, we supported the blood lead component of the Second National Health and Nutrition Examination Survey, the results of which, published in the New England Journal of Medicine, were of major value to EPA in its recent decision to maintain strict controls on the lead content of gasoline. Our primary interest in lead relates to its impact on calcium and vitamin D absorption and metabolism, further evidenced by our support of a significant portion of the elegant research on the subject by Dr. Hector DeLuca and his colleagues.

As a regulatory Agency, FDA's primary responsibility is to the nation's consumers. To carry out this responsibility, the Agency must have knowledge of consumer needs for information and the best means for providing this information. The Division of Consumer Studies is the only research unit at the Federal level devoted directly to consumer research as it pertains to nutrition. The unit was established in 1972 and is primarily involved in the study of consumer behavioral changes over time as influenced by Federal and other programs such as nutrition labeling, warning labeling and the current effort to reduce the sodium content of the food supply. The summary of FDA's nutrition research that follows is only a portion of FDA's total research on foods which includes comparable efforts in such areas as toxicology, microbiology, food technology, packaging technology, and food analytical chemistry. FDA's total budget in the food area is approximately 100 million dollars of which approximately twenty-five percent is spent on research. Many of the research programs are highly interrelated and significant sharing of services and equipment across research programs occurs. Similar sharing of services and

equipment occurs between regulatory programs and research programs provides an opportunity for more effective use of resources which would not be possible if these missions were not tied together in a single Agency.

FDA Division of Nutrition

By

John Vanderveen, Ph.D.

DIVISION OF NUTRITION
NUTRITION RESEARCH
FOOD AND DRUG ADMINISTRATION

This paper describes the statutory basis for nutrition research at the Food and Drug Administration (FDA), some goals of the nutrition research program, and key research activities.

Introduction

The FDA is the Federal agency principally responsible for administering the provisions of the Federal Food, Drug and Cosmetic Act, which was originally signed into law in 1938. The agency quickly recognized that nutrition research was important to the fulfillment of its mission under the act. Nutrition research at FDA commenced in 1938 and has continued to the present as an organizationally recognized unit. Recent amendments to the act as well as other Congressional activity in the area of nutritional impact on food safety has served to reinforce FDA's view of the importance of nutrition research.

There often is the misconception by those outside the agency that the Food, Drug and Cosmetic Act narrowly constrains nutrition research at FDA solely to the support of regulations such as nutrition labeling and food standards. Certainly these are important aspects of research in the FDA Nutrition Program, but they are by no means the only significant goals. The act is broader than this narrow view would suggest, and a broad breadth program of nutrition research is required. For example, nutrition research is needed to:

- o monitor and influence technological trends that may impact on the nutrient quality of the American food supply;
- o provide a rational basis for use of the food supply as a vehicle for nutritional management of disease and injury; and
- o establish a resource for efforts to influence dietary trends that may impact on the nutritional health status of the American public.

FDA's strategy for achieving these goals is to maintain a high quality research capability in three major domains: nutritional quality and safety of the food supply, nutrient analysis to assist in the establishment of criteria to protect against misleading food label information or fraud, and assessment of the nutrition status of the American population. The first area includes studies on nutrient bioavailability, interaction between nutrients and other food components or contaminants, nutrient toxicity, nutritional determinants of behavior. Surveillance analyses to identify potential problems requiring establishment of labeling criteria, and development of improved analytical techniques allowing rapid quantitation of nutrients in the wide range of foods available in the American food supply dominate research in the second area. Studies in the third area are used to establish health status and nutrient intake of the general population and specific subpopulations, and to provide data on the dietary management of disease or abnormal physiological states.

It is evident that the nature of FDA's role in nutrition research can be succinctly summarized as functioning in the applied research world with technology transfer as the end result.

Key Research Areas

Lipids. Public health may be favorably or adversely affected by new food processing methods and new food ingredients that alter the lipid or fat content of the food supply. The alteration may be in the form of decreases in essential fatty acids, new structural forms (e.g., sucrose polyester and trans-fatty acids), or increased use of fats and oils from unaccustomed sources (e.g., marine oils). The nutritional and metabolic consequences of these changes is largely unknown. In many cases methods currently do not exist for detecting or quantitating these substances in food or in body tissues and fluids, thus hindering studies on the health consequences of their presence or absence. Some recent work in this area at FDA has been the development of techniques to isolate and identify sterol compounds in vegetable oils, and the use of sterol and fatty acid distribution patterns to detect blending or substitution of fats and oils. The use of modern chromatographic techniques has raised questions about the traditional wisdom that cholesterol only occurs in animal fat, because sterol analysis of vegetable fats has revealed a component that appears to be cholesterol per se. FDA research efforts seek to chemically identify this substance with certainty because of the potential health impact for persons who must control their cholesterol intake. Among planned studies is one on the metabolism of trans-fatty acids and of polyunsaturated, long chain natural fatty acids. These studies have been initiated by development of methods to detect and distinguish between cis- and trans-fatty acid isomers.

Nutrient Interactions. Nutrient interactions modify dietary nutrient requirements and bioavailability. This impacts on FDA food fortification and diet supplement policies and regulations. Interactions among nutrients, and between nutrients and other food components, also affect the toxicity of hazardous elements, thus impacting on agency food safety activities. Agency research on nutrient interactions, such as the availability of zinc in soy-based foods, is an example of research technology that is immediately transferred for the public benefit. FDA has developed a model reference diet for Japanese quail that is successfully being used to examine questions of nutrient interaction. This model has been used, for example, to examine the relative toxicity of organically bound cadmium in oysters vs. inorganic cadmium, without interference from the high mineral content of oyster meat. The study results showed that low mineral content enhances cadmium uptake in the jejuno-ileal section of the gastrointestinal tract. Earlier work at FDA has shown that zinc supplementation reduces accretion of cadmium. Efforts are continuing to determine the extent of this effect, as are studies to determine effectiveness of other mineral nutrients, such as iron, in inhibiting accretion of lead and other heavy metals. The quail model has also been used to demonstrate that texturized vegetable protein adversely affects iron absorption and storage but has no effect on hemoglobin

formation. Other agency studies in this area include examination of the effects of soy products on zinc requirements during growth, and development of a reference diet for rats that is analogous to the quail reference diet. FDA is also examining the bioavailability and interactions of minerals in natural organic matrices vs. inorganic forms. In our Cincinnati laboratories plants are grown in media containing radiolabeled traces of the mineral to be studied. The tracer becomes incorporated into the plant material which is then harvested and used as feed.

Bioavailability. Food fortification and food safety policies are also influenced by data on bioavailability and nutrient toxicity, two areas of investigation at FDA that are closely allied to the nutrient interaction work. The bioavailability studies are aimed primarily at assessing the effect of new fabricated foods on the nutritional quality of the food supply, with special emphasis directed at the quality of new protein sources. The studies seek to address issues such as the quality of the protein itself and the effect of a particular protein source on availability of other nutrients. An additional concern that is receiving increased emphasis is the presence of "anti-nutritional" substances, such as proteinase inhibitors, in alternative protein sources.

Nutrient Toxicity. Section 411 of the Food, Drug and Cosmetic Act markedly restricts FDA's authority to regulate the use of nutrients in food, and in particular, nutrient use in dietary supplements. However, FDA can limit nutrient use when clear evidence of nutrient toxicity exists. The principal objectives of nutrient toxicity research at FDA are to assess the hazards of increased nutrient consumption, to determine the bioavailability of heavy metals present as contaminants in dietary supplements, and to evaluate the efficacy of mineral nutrients to inhibit accretion, and therefore toxicity, of heavy metals. Animal models have been developed to accomplish the first objective and work will soon begin to evaluate the toxicity of manganese, selenium, and multinutrient combinations. The initial research applicable to the second objective was the examination of bone meal samples for the level of lead contamination. The average lead level equaled the upper limit of safety for lead in calcium phosphate set by Food Chemicals Codex (5 parts per million). The maximum level found was about three times this level. Studies are now being planned to evaluate the bioavailability of lead at this level in bone meal. This work on lead in bone meal is another example of research that is "transferred" quickly for the public benefit. Studies on zinc and iron inhibition of cadmium and lead absorption, respectively, were noted in the discussion of nutrient interaction. Related work has examined other dietary factors influencing lead toxicity, including total calories, calcium, fat, protein, and vitamin D status. Because the observed toxic effects are influenced by nutritional status, the effects can be thought of as another aspect of nutrient toxicity.

Behavior. Food safety considerations are predicated not only on potential toxicity of food ingredients, but also on estimated consumption. Consumption behavior, and behavior in general, may be

affected by nutrients and other ingredients in food. Behavior in turn has an effect on nutrient and food intake. These interactions may compound other factors affecting nutrient status. FDA is sponsoring a contract effort that has developed an animal model useful in searching for behavioral effects of nutrients and additives. Interest in this area originates from investigations which have demonstrated that diet composition profoundly affects certain biogenic amines in the central nervous system. Testing of specific substances of interest, such as sucrose and benzoic acid, will begin soon. The effects of sensory inputs on food consumption patterns are being examined in-house. Surgical deafferentation of oral somatosensation and taste is being used to investigate diet selection in rats. Preliminary data suggest that taste impaired rats select a higher proportion of protein in their diet than do normal rats. Somatosensorally impaired rats reacted no differently than control rats to amino acid imbalanced diets, but they did not compensate for intra-gastric protein supplementation by reducing oral protein intake as did control animals.

A number of peptides, such as somatostatin and endorphin, have been implicated in the control of food intake. Trial experiments showed that somatostatin caused selective reduction in protein intake when rats were allowed to chose between diets containing primarily protein or carbohydrates. These studies are continuing and include the development of techniques to measure somatostatin receptors in target tissues, as well as examination of nutrient intake effects of other peptide neurotransmitters.

Analytical Methodology. More and more formulated foods are being developed as the sole source of nutrition for persons with various medical problems. In addition to the other nutritional considerations that these foods present, they may contain refined protein that is nutritionally debased. Many substitute foods are being developed that also incorporate refined protein. As a consequence of these advances in technology, current analytical methods for determining nutrient content and quality of foods are often inadequate. Thus, methodological research in nutrient analysis plays a critical part in FDA's role as a regulatory agency. It is this research that allows FDA to establish criteria that protect against misleading or fraudulent food labeling. Current FDA research includes development of chemical methods for vitamin analysis to replace the existing bioassays which are both cumbersome and time consuming. Improved instrumental methods for mineral analysis are also being investigated. Efforts are being made to refine the protein efficiency ratio (PER) method for determining protein quality, or to replace this method with one that is more broadly applicable. FDA is completing an international collaborative study to compare current analytical methods for determining "fiber" in foods with a method developed at FDA that incorporates the best features of these methods. A similar effort is anticipated for phytate methodology. FDA has participated, and continues to participate, in collaborative studies to improve methodology for vitamins, minerals, and macronutrients (e.g., carbohydrates) as well. In progress is an effort that involves collaboration with the infant formula industry to identify the most

accurate and reproducible methods for measuring vitamins and minerals in such formulas and similar foods.

Clinical Nutrition Assessment. Clinical nutrition assessment research, or efforts to assess the nutrition status of the American population, is fast becoming a cornerstone of nutrition research at FDA.

For over a decade FDA has conducted an annual survey of the American food supply, analytically determining the level of certain organic contaminants, heavy metals, and essential minerals. This is the only such survey wherein foods are annually gathered nationwide in a consumption-based design. This survey, called the Total Diet Study, has a component known as the Selected Minerals in Foods (SMIF) Survey. Sodium, calcium and iron are among the 11 essential minerals that are monitored. The Total Diet Study has recently been redesigned by the Division of Nutrition using the most recent data bases on food consumption. The redesigned study will permit FDA to determine: yearly trends in the mineral (and heavy metal and contaminant) content of 234 individual foods that are representative of the American diet; daily intake and adequacy of each of the 11 minerals for each of eight age-sex groups; yearly mineral intake trends for each of the age-sex groups; and major food sources of the minerals for each sex-age group.

Food fortification is a recognized public health measure for reducing the prevalence of deficiency diseases in the population. Through its project on Food Consumption, Diet and Health, FDA monitors and analyzes various large data bases on food composition, eating practices, nutrient intake, and the nutritional and health status of population groups. In addition to the SMIF Survey run by FDA, the agency utilizes data bases generated by USDA (Nation-wide Food Consumption Surveys), Market Research Corporation of America (frequency-of-eating data), and the National Center for Health Statistics (National Health and Nutrition Examination Surveys -NHANES). The recently published paper on blood lead levels (N. Eng. J. Med. 307 (10)573-579, 1982) is an example of FDA's support of NHANES and the use of the resulting data. FDA is now in the midst of a congressionally mandated analysis of NHANES II data relative to zinc, iron and folacin. The thrust of this research is to address specific questions that have arisen about fortification policies as they are applied to cereal grain products.

Nutritional anemia is a recognized public health concern for some subpopulations in this country. FDA has contracted a number of studies that are intended to provide a data base on iron in human nutrition for evaluating current iron fortification policies. These studies seek to determine: the efficacy of iron fortification in preventing the development of anemia and in maintaining iron status; the absorption of iron by patients suffering from overload syndromes, by their immediate relatives, and by alcoholics; racial differences in response to iron supplementation; the relationship of iron status to mental performance in preschool children; and the bioavailability of different iron salts. This latter study will compare rat bioassay, radiotracer absorption by humans, and in vitro methodologies.

Perhaps the most publicly visible product of FDA's clinical nutrition assessment efforts is the Agency's major effort to encourage the food industry to voluntarily lower the sodium content of processed food and to provide consumers with quantitative sodium declarations on food labels--the program having been implemented to favorably affect the prevalence, severity and management of essential hypertension. A key feature of this effort is an ability to do the research necessary to measure its success. FDA nutrition research activities include a number of continuing efforts that contribute to this capability. One, the SMIF survey, has been discussed here. Others are included in the descriptions of work performed by FDA's other nutrition research unit, the Division of Consumer Studies.

FDA also seeks to maintain contract capabilities to provide state-of-the-art scientific analyses by expert task forces. These analyses provide expert review of current scientific knowledge, and consensus conclusions on major actual or potential nutrition problems of interest to the agency, e.g., the effects of dietary calcium and phosphorous on bone homeostatis and its relevance to fortification policies. A separate contract focuses on pediatric nutrition problems, e.g., maximum and minimum nutrient levels in infant formulas. FDA maintains in-house surveillance of efficacy and safety problems associated with medical foods, those foods that are intended to support dietary management of diseases or other abnormal physiological states. The agency has had expert analyses provided under contract in the past on medical food problems, and it will seek such advise again when necessary.

Conclusion

The knowledge gained from FDA's nutrition research efforts is applied through a four-step mechanism to implement whatever changes are necessary to successfully reach national nutrition objectives. First, FDA maintains communications with industry to promote nutritionally sound food processing techniques and adequate food labeling, and with consumers to promote nutritionally rational dietary habits. Second, FDA uses its powers of persuasion to move industry to act voluntarily with respect to changes perceived necessary for food labeling and manufacturing. Third, the agency formulates policies delineating the standards by which it will evaluate industry actions that affect the nutritional quality of the food supply. Finally, FDA promulgates, when necessary, specific regulations that require industry to either label or manufacture food, or both, in a fashion that the agency believes will lead to achievement of national nutrition objectives.

To summarize and reiterate, FDA maintains a broad nutrition research capability in nutritional quality and safety, nutrient analysis, and clinical nutrition assessment in order to: influence the nutritional quality of the American food supply; enhance the biomedical basis for nutritional management of disease or injury; to influence dietary trends into beneficial channels; and to support actions that are statutorily mandated. While some of this work is necessarily basic research, most is applied and is aimed at transfer of technology to the public domain.

FDA Division of Consumer Studies

By

Raymond Stokes, Ph.D.

DIVISION OF CONSUMER STUDIES
NUTRITION RESEARCH
FOOD AND DRUG ADMINISTRATION

Introduction

The Division of Consumer Studies in the Food and Drug Administration (FDA) engages in these broad research activities: (1) consumer research which obtains data through surveys and experiments by direct contact with the consuming public; and (2) market research which obtains data from the retail market place, usually in the form of sales volume.

The FDA must be responsive to the needs and desires of the consuming public. To do this the needs and desires must be known. The best way to accomplish this is through sound scientific consumer and market research. Similar research methodologies are indispensable in evaluating regulatory actions and consumer education programs. The research is of a pragmatic, action oriented nature designed to assist management in decision making and in evaluating the success of agency programs.

CONSUMER RESEARCH

Nutrition Labeling

In December of 1969 the White House Conference on Food, Nutrition and Health recommended that more nutrition information be made available to consumers. In response, FDA initiated a nutrition labeling program which resulted in a preliminary proposal in 1972 and a final regulation in 1973 with an effective compliance date in July of 1975.

In 1978 the FDA, USDA and FTC held hearings on food labeling and concluded that current nutrition labeling, a good first step, may need revisions to make it more understandable and useful to consumers.

Also in 1978, FDA conducted a food labeling survey with a national probability sample and concluded that:

1. The current nutrition label is seen as complex and technical terminology is not well understood. Uncertainty is expressed about how to use the information.

2. Many people are concerned about the safety of the food supply and wish to avoid constituents which may be harmful.

3. The public is more interested in information about calories, sodium, fat and sugars than they are about vitamins and minerals.

In 1980 FDA sent mail questionnaires to the American Institute of Nutrition, companies in the food industry and to a FDA mailing list of consumers. There was remarkable agreement in the opinions of these three groups which indicates that the belief that there is widespread disagreement and controversy on basic nutrition matters is not entirely true. Top priority nutrition information included: calories, sodium, protein, total carbohydrate, total fat, iron and calcium. A lower priority was placed on cholesterol, fatty acids, potassium, sugars, fiber, Vitamin A and Vitamin C. It was agreed that simplicity and ease of understanding should be major goals of any revision of the nutrition label.

In 1980 FDA signed a contract with Robert P. Gersin Associates, a New York design firm to assist in the design of an array of nutrition labeling formats to be subjected to consumer evaluation. The design of alternate formats has been completed and will be presented at a public meeting to be held in Washington, D.C. on December 2, 1982. A research plan to evaluate the communication effectiveness of the formats will also be presented. The core of the research will utilize the eye camera which is a precision measuring device. It measures the length of time (to 1/60 of a second) the pupil of the eye focuses on a very small area in the visual field, the sequence of focuses, whether the eye rechecks information, and also reveals what the eye does not see. People who have diet-related health problems such as hypertensives, diabetics and those with cardiovascular disease will be included in the sample. The elderly and undereducated will also be included. The research to evaluate the formats should begin in the summer of 1983 and finished about one year and a half later.

1982 Consumer Food Survey

The primary purpose of this research is to establish a baseline against which subsequent surveys can be used to evaluate changes in knowledge, attitudes and behavior relating to sodium consumption and hypertension.

Telephone interviews were conducted in the fall of 1982 with a national probability sample of approximately 4,000 adults. The research was jointly sponsored by the National Heart, Lung and Blood Institute. Major topics include:

1) consumer awareness of relationships between diet and health, with emphasis on sodium, fats and cholesterol, and on hypertension, other cardiovascular diseases, and cancer

2) awareness of and usage of label information about salt and sodium content of foods; preferences regarding terminology

3) shopping, cooking, and consumption habits with regard to salt and sodium

4) degree of concern with personal levels of consumption of sodium and of fats and cholesterol

5) knowledge of hypertension, including causes, symptoms, effects, and treatment

The two agencies plan to publish the data from the survey as a series of reports to be released over the next six months. The first FDA report, "The Public Response to Labeling of the Sodium Content of Foods," has been completed. It reveals that active concern with sodium consumption, as measured by the number of people claiming to use label information to limit consumption, has nearly tripled since 1978, from 14% to 40%.

Both verbal descriptors of salt or sodium content (e.g., "salt free," "low sodium") and quantitative declarations of sodium content ("sodium content -- x mg per serving") are familiar to more than three-fourths of consumers and are nearly universally seen as useful. However, a majority of the public feels there are too many different verbal descriptors available and that quantitative declarations are not as useful as they might be due to technical terminology or lack of knowledge of what reasonable goals might be in terms of mg of sodium consumed daily.

FDA plans to repeat this survey annually for several years as part of the Agency's research to evaluate the effectiveness of the sodium program.

Vitamin and Mineral Survey

So far as we know, this survey is unique and should generate data which will be extremely useful to the Agency. While both NHANES and USDA's food consumption surveys obtain some information on vitamin and mineral consumption, it is not in sufficient detail to be of maximum use to FDA.

In 1981 a telephone survey was conducted with about 3,000 households. A random digit dialing technique was used to generate a national probability sample of listed and unlisted telephone households. On the basis of an enumeration of all adults residing in the household at the time of the interviewer's screening call, a stratified sample of 1,000 adults was randomly selected in each of three age groups: 16-24, 25-64, and 65 and over. Age stratification was employed in order to produce a minimum sample size in each age group for analysis purposes. Interviewers were dieticians trained in telephone interviewing techniques for the survey. They also edited and coded the consumption data.

In designing the survey, the need was recognized to have respondents report vitamin usage on a brand-by-brand basis. Furthermore, since respondents would not necessarily be knowledgeable about the composition of the supplements or the units of measure for individual nutrients, the survey design called for respondents to bring their supplement bottles to the telephone and to read nutrient/mineral composition and potency information from the label. For purposes of analysis and interpretation of the consumption data, the questionnaire also covered circumstantial information of direct and indirect relevance to supplement use, such as sources of influence, whether taken under a physician's care, general dietary practices, snacking habits, vegetarianism, height and weight, a self assessment of current state of health, and respondent's perception of degree of personal control over health.

Preliminary tabulations of the data are encouraging with respect to the quality of interview obtained with older respondents and the breadth and depth of detail achieved in all age groups. For example, reported daily intake and label nutrient composition data were obtained for over 1,150 vitamin/mineral brands reported as currently used by approximately 40% of each age group. An additional 100 brands not reported in adequate detail during the interview were well enough identified by respondents to allow the brands to be purchased at retail for label analysis purposes. Within the age stratum 65 and over, the modal age among respondents interviewed was 70; 10% of the stratum was aged 80 and over and the oldest respondent interviewed was 95.

Household cooperation was 87.5% (12.5% refused) during the telephone screening call to enumerate household members and select a survey participant. In the main interview, 79.8% of supplement users expressed willingness to bring their products to the telephone and read label information. Data on intake and the nutrient profile for each reported brand of supplement ultimately was obtained for 74.1% of the users. The difference between users willing to report and those actually providing complete data was 5.7%. Generally this consisted of respondents who provided complete nutrient information for most of their supplements but may have missed a supplement that had been used up and the bottle discarded, or who found that a supplement was physically located elsewhere.

The 74.1% completion rate included 1% of users who were unable to complete the interview during the initial phone call and participated in a second phone interview at a more convenient time. Also included were 6% of the users who were not willing or did not have time by phone to complete the detailed section of the interview dealing with the nutrient composition and who agreed to provide the necessary information on a mail questionnaire. Mail returns were received from 25% of this subgroup. Finally, 83.7% of users in the survey reported nutrient composition for at least one of the supplements they were taking.

A report of an analysis of quantitative nutrient intake is in preparation. Also, a multivariate analysis of the characteristics of supplements users is currently underway.

It is hoped that this survey can be repeated every two or three years to track the anticipated growth in usage of vitamin and minerals.

MARKET RESEARCH

Food Label and Package Survey (FLAPS)

The food industry is highly dynamic and the information available to consumers is constantly changing. The FLAPS research mechanism is FDA's way of keeping informed about these changes over time, especially nutrition information, quantitative sodium labeling and ingredient listing. However, all other information of interest on the label is entered into FDA's data base.

The sample consists of approximately 1700 food brands and is representative of packaged/processed foods sold in grocery stores throughout the United States. Included are shelf stable, refrigerated and frozen products in about 200 product classes representing 50 major processed food groups.

The data base of information from the food labels is analyzed by FDA in terms of the national sales volume of the brands in the sample. The sales information is obtained under contract with the A. C. Nielsen Company. Terms of this contract prohibit disclosure of the actual sales or market position of individual brands or product classes.

FLAPS I conducted in 1977 found that 40% of the packaged processed food supply was nutritionally labeled. FLAPS II conducted in 1979 found that nutrition labeling had increased to 43%. Analysis of FLAPS III data is in progress.

Field work for FLAPS III was completed during the months of February through August, 1982. Tabulation of quantitative sodium labeling has been completed, and a report issued in December 1982 showed that 19% of packaged food sales now have quantitative sodium information. The corresponding figure in 1980 was 13%. A special FLAPS survey covering sodium only will be fielded in January 1983, with results to be reported by July.

DEPARTMENT OF DEFENSE

DOD Programs with Nutrition Research Components

By

Lt. Col. David Schnakenberg, Ph.D.

DOD PROGRAMS WITH NUTRITION RESEARCH COMPONENTS

A series of interrelated decisions by the Army in FY 1977-78 and specific congressional action in FY 1979 and FY 1980 resulted in a significant reduction in the scope of DoD nutrition research programs. Certain resources at Letterman Army Institute of Research (LAIR) at the Presidio of San Francisco, CA, that previously were committed to nutrition research activities of national as well as military interest were either transferred to the U.S. Department of Agriculture (USDA) or reassigned to higher priority Army medical research programs outside the field of nutrition. Examples of these nutrition research activities which were perceived to be the primary domain of Federal agencies other than DoD included the development of biochemical methods to assess nutritional status, establishment of nutrient requirements for health and prevention of chronic disease, and the study of the nutritional aspects of certain metabolic disease states.

Nutrition research components are continuing to be incorporated into the various basic and applied mission-oriented programs of the U.S. Army Medical Research and Development Command. For example, at the U.S. Army Institute for Surgical Research in San Antonio, TX, studies are conducted to define the effects of thermal injury on endocrine function and on the metabolism of proteins, carbohydrates and fats. These studies will improve our knowledge for the optimal nutritional support of burn injury in soldiers. The isolated adipocyte is being used to determine the metabolic response of adipose tissue following thermal injury. A computer graphics program has been developed to aid rapid evaluation of the nutritional status of critically ill burn patients and to tailor parenteral and/or enteral diets for the specific patient. At the U.S. Army Medical Research Institute of Infectious Diseases at Fort Detrick, MD, studies are continuing, but at a somewhat reduced level of effort, to develop nutritional and hormonal therapy to reduce weight loss and protein wasting associated with infectious diseases of particular importance to the military.

DoD Food Research Programs conducted at the U.S. Army Natick Research and Development Laboratory at Natick, MA, include food and behavioral sciences approaches to evaluate the effects of new food processing techniques and long-term storage on consumer acceptance and nutrient content in foods for military rations. The effort also includes research on methods for the evaluation of texture, flavor, appearance, etc., of foods and how these variables provide individuals with perceptual and hedonic information that is critical to food choice decisions.

The Navy Medical Research and Development Command's mission related programs includes certain nutrition related studies such as the relationship of ascorbic acid to sonor operator performance effectiveness, the assessment of trace metal nutritional status in Navy recruits to establish occupational base lines, and the evaluation of electrolyte requirements associated with heavy physical performance in cold weather environments.

A workshop on the Nutritional Requirements of Military Personnel in Protective Clothing was held in Washington, DC in June 1982. The workshop was conducted by the National Research Council and supported by the U.S. Army Medical Research and Development Command. A report of the International Nutritional Anemia Consultative Group (INACG) entitled "The Effects of Cereals and Legumes on Iron Availability" was published in June 1982. This study was jointly supported by the Army, USDA, FDA, and USAID.

A military nutrition research component is currently being established at the U.S. Army Research Institute of Environmental Medicine at Natick, MA. The mission of this group will be specifically directed to nutrition related problems of feeding in tomorrow's battlefield and the critical end-point of this research will be the effective performance of physical and mental tasks under sustained combat operations. Close liaison will be established with the nutrition research programs of the other Federal agencies to develop the nutrition research technology base and to avoid duplication of effort. To assist in the planning effort, a Committee on Military Nutrition Research has been established with the National Research Council.

VETERANS ADMINISTRATION

VA Nutrition Research Programs

Overview

By

Victor Herbert, M.D., J.D.

REPORT OF VA NUTRITION RESEARCH PROGRAMS

The Veterans Administration's primary responsibility is to care for those who have borne the battle and for the survivors of those who died. There are 174 VA Medical Centers (VAMC), of which 130 have substantial research programs, usually under an Associate Chief of Staff for Research (ACOS/R&D) aimed at constantly improving the quality of health care for veterans, by constantly improving diagnosis and therapy. The VA does not compartmentalize its research components into "This is nutrition - that is endocrinology - that is heart disease, etc.," but a 1982 review delineated substantial nutrition components in 50 of the 130 VA Medical Centers with research programs. The full-time equivalent of approximately 300 M.D.s, and Ph.D.s, plus 600 support personnel (research technicians, registered dietitians, nurses, secretaries, etc.), are engaged in VA nutrition research, many being "WOC" personnel ("without [VA] compensation"), spending one to three years under the direction of outstanding VA researchers at various VA Medical Centers, as visitors from academic institutions in the U.S. and abroad. Some of the WOC personnel are unpaid volunteers, but a number have salaries paid variously by affiliated medical schools, the NIH, the World Health Organization, the International Atomic Energy Agency, and many other organizations. The VA provides some of them with meals and occasionally housing, but no other funding. They add to the quality of VA patient care at minimal to no cost to the VA.

VA nutrition research is not centralized in the sense that it is not directed from the VA Central Office; the system is similar to that in the University of California system with its many campuses. Investigators in the field work in areas which have both immediate and long-term benefits in improving the quality of veteran patient care and keep the VA in the forefront of applying the latest fruits of nutrition research to the day-to-day care of veteran patients. They secure funding both from VA Central Office and from outside agencies; many are affiliated with medical schools and seek funding through the medical schools which then request funds of NIH and of various private foundations. Some VA nutrition research is supported, for example, by funding from the American Cancer Society, the Arthritis Foundation, the American Heart Association, the American Diabetes Association, the National Dairy Council, and other outside philanthropic agencies which support nutrition research related to their interests.

In VA Central Office, the overall nutrition research program is run by Dr. Hollis Boren, who is Associate Chief Medical Director for Research and Development, and Dr. Richard Greene, who is Director of the Medical Research Service. VA Central Office has a Clinical Nutrition Advisory Group (CNAG), started by Dr. Paul Haber, now under the joint direction of Dr. Neil Otchin and Edwina McDonald, which supplies nutrition advice to the 174 VA Medical Centers. At the September 1982 annual meeting of that group, a basic nutrition evaluation was delineated as desirable for every entering patient in every VA Medical Center. There are opportunities for those of you affiliated with institutions which have a VA nearby to work with the VA in collecting this information and using it effectively for the benefit of our patients and for the expansion of nutrition knowledge. The various VAMCs engage in nutrition education of VA patients, and, during National Nutrition Week, also to the public entering VAMCs.

We cannot present here in two hours all fifty VAMC nutrition programs and have selected five VA nutrition researchers to represent their VAMCs. First, I wish to draw to your attention several other VA nutrition research units engaged in mineral metabolism: the programs of Ananda Prasad at the VAMC in Detroit, Herta Spencer at the Hines VAMC in Illinois, and Marcel Conrad at the VAMC in Birmingham, Alabama (affiliated with the University of Alabama Medical School where Dr. Charles Butterworth yesterday showed us an entire nutrition research building under construction).

Dr. Prasad's laboratory has been involved with studies of zinc metabolism in animals and humans and has generated important information for two decades. His laboratory has been engaged in defining marginal zinc deficiency. A pure zinc deficiency of marginal degree is induced in human volunteers by dietary means, and various zinc-dependent parameters are measured throughout the baseline, zinc depletion and zinc repletion phases. Many biochemical parameters are being assessed which may eventually define marginal zinc deficiency. Over 100 enzymes are now known to require zinc for their functions. His studies show that activities of some zinc-dependent enzymes were affected adversely in zinc deficient tissues of experimental animals, suggesting that the major role of zinc is probably enzymatic in nature. He also showed that deoxythymidine kinase is a zinc-dependent enzyme and that its activity decreased very rapidly in newly synthesizing collagen connective tissue, once experimental animals were made zinc deficient. This was accompanied by a decrease in DNA and protein synthesis.

His studies have particularly focused on the role of zinc in testicular function. In animal and human models, it has been established that the adverse effect of zinc deficiency is on the end organ, namely the testis, and that the pituitary-hypothalamic axis remains intact. Further studies are being conducted in experimental animals, in order to understand the mechanism by which zinc may affect testicular functions.

Recently, it was learned that zinc plays an important role in cell-mediated immunity. Thymus decreases in size as a result of zinc depletion. Many functions of thymic-dependent cells (T-cells) are affected adversely due to zinc deficiency. He is currently investigating the role of zinc on natural killer cells and Interluken I and II. Effects of zinc deficiency on nucleoside phosphorylase, an enzyme considered to be important for T-cell function and zinc concentration of lymphocytes are being assessed.

Herta Spencer's facility is a ten-bed metabolic research unit fully occupied throughout the year. The studies are carried out under strictly controlled conditions; diets are prepared in the kitchen of the metabolic ward and there is complete collection of excreta. The patients are supervised 24 hours a day by a nursing staff highly experienced in metabolic research. All analyses of the diet and biological samples are carried out in laboratories of the metabolic unit. The unit is involved in studies of mineral and trace element metabolism in humans, concerned particularly with

long-term studies of calcium, phosphorus, magnesium, zinc, fluoride and iron. The minimum duration of each study is 30 days, but the studies are frequently carried out for many months. In addition to studies of the metabolism of any given single mineral or trace element, the main emphasis of the investigations are studies of the availability and interaction of certain minerals with other minerals and of minerals with trace elements. Extensive studies are carried out on changes of mineral metabolism in aging, which is one of the selected priorities of VA research, and on the calcium requirement. In all studies, complete metabolic balances of the respective minerals or trace elements are determined in order to obtain background information on the constancy or variability of the metabolic status of the subject under study. Tracer doses of radioactive or stable isotopes, such as ^{47}Ca, ^{28}Mg, ^{26}Mg, ^{59}Fe, ^{65}Zn and ^{85}Sr are given to characterize intestinal absorption of a given mineral or trace element under specific study conditions. Radioisotopic assays of plasma, urine and stool are carried out in the laboratory of the metabolic unit. The majority of the studies are carried out in fully ambulatory, normal adults who do not receive any medications; however, studies are also carried out in patients with structural and functional abnormalities of the skeleton and various types of metabolic bone disease, such as osteoporosis, osteomalacia, hyperparathyroidism, hypoparathyroidism, and other conditions. Mineral balance studies are carried out in the active phase of these conditions and during treatment, in order to evaluate objectively the metabolic effects of a specific therapeutic regimen. Other types of studies of mineral and trace element metabolism, such as studies of calcium, magnesium, zinc, and fluoride metabolism, are carried out in patients with chronic renal failure who do not receive any medications and who are not undergoing dialysis. The studies in the Spencer unit are among those being used by the Food and Nutrition Board in its deliberations which will result in the 1985 RDA for calcium. As you know, there is question if the RDA for calcium is adequate or should be altered; studies such as those being carried out in units like Dr. Spencer's are crucial to such deliberations.

The current research on iron absorption, excretion and metabolism being carried out in Marc Conrad's unit focuses on mechanisms by which the intestinal mucosal cell regulates absorption of iron and other divalent metal cations. He specifically identifies ferrous and ferric iron complexes within intestinal absorptive cells using electron microscopy; all identifiable iron is measured. Sequential studies using specimens of gut obtained at interval after exposure to iron permit observations of the entry and storage within the absorptive cells and their ultimate transfer into the lamina propria; this is done by intestinal biopsy of volunteer patients. The quantity of iron in intestinal absorptive cells varies directly with the status of iron absorption. The postulate as to how this works is tested by direct examination using direct staining electron microscopy; he is currently attempting to develop chemical methods permitting measurement of the non-ferritin total iron binding capacity and the unsaturated iron binding capacity of the intestinal mucosa.

Among the 50 nutrition research units within the VA system there are studies which range across every facet of nutrition - vitamins, minerals, hormones, carbohydrates, fats, proteins and water. Much work is being done on electrolyte balance, and in total enteral and parenteral alimentation, including problems which arise therewith and the solutions to those problems.

The VA Research and Development Program has been reviewed by Marguerite Hays (Clin. Res. 31:28-30, 1983), with comments by a group of VA Physicians (Clin. Res. 31:31-33, 1983).

VA Medical Center

Lexington, Kentucky

By

James Anderson, M.D.

Plant fiber intake improves management of the metabolic disorders common among veteran patients. Fiber intake benefits patients with diabetes mellitus, obesity, hypercholesterolemia, hypertriglyceridemia, hypertension, or reactive hypoglycemia. Since 1974 the metabolic effects of fiber-rich foods on the physiology and metabolism of nutrients in humans and animals has been examined. Initially the plant fiber content of common American foods was measured since these data were not available. The short-term effects of fiber intake on nitrogen balance and short-chain fatty acid production as well as the long-term safety and nutritional effects of high-fiber diets were studied.

Diabetes. With high-carbohydrate, high-fiber (HCF) diets, insulin requirements of lean adults are 75 percent lower than requirements on conventional diabetic diets. Weight-reducing HCF diets lower insulin needs of obese patients by 88 percent. HCF diets lower serum cholesterol concentrations by 30 percent and fasting serum triglycerides concentrations by 14 percent. High-fiber maintenance diets sustain these beneficial effects for outpatients for up to 8 years. Aside from increased gas production, no adverse effects on gastrointestinal function, vitamin or mineral status were observed. Higher carbohydrate, higher fiber diets are now endorsed by national diabetes associations in the United States, Canada, Great Britain, and Australia.

A high fiber intake lowers postprandial plasma glucose concentrations, increases tissue insulin receptor number, facilitates intracellular glucose metabolism and, via short-chain fatty acid released from the colon, attenuates hepatic gluconeogenesis. The high fiber intake complements the effects of complex carbohydrate intake and fat-restricted diets.

Obesity. High-fiber, weight reducing diets are accompanied by greater satiety and less hunger than are low-fiber, weight-reducing diets providing equivalent energy. HCF weight-reducing diets produce less nitrogen loss, less hepatic dysfunction, less ketonemia and smaller rises in serum uric acid concentrations than very low calorie diets. The long-term effectiveness of these diets are being assessed. Sucrose polyester, a nonabsorable fat in the form of mayonnaise or margarine, appears to complement the effectiveness of HCF weight-reducing diets.

Hypercholesterolemia. Water-soluble fiber intake has hypocholesterolemic effects. After examining the palatability and effectiveness of several water-soluble fibers and high soluble-fiber foods, we have focused on the effects of oat bran. Oat-bran intake selectively lowers serum low density lipoprotein (LDL) cholesterol concentrations without altering serum high-density lipoprotein (HDL) cholesterol concentrations. Oat-bran intake thus increases the HDL to LDL cholesterol ratio by 50 percent over short-term periods and by 100 percent over long-term periods. Intake of 100 g of oat bran daily lowers serum cholesterol concentrations by 20 percent without alter-

ing the intake of fat or cholesterol. Oat bran intake increases fecal bile acid excretion by 50 percent. Animal studies suggest that short-chain fatty acids absorbed from the colon attenuate hepatic cholesterol synthesis.

Hypertriglyceridemia. For patients with average fasting serum triglyceride concentrations exceeding 1000 mg/dl, weight-maintaining HCF diets lower triglycerides by 80 percent on the Special Diagnostic and Treatment Unit. Long-term intake of high-fiber diets lowers fasting serum triglycerides by another 10 percent so these patients sustain triglycerides which are 90 percent lower than initial values.

Hypertension. Preliminary studies indicate that HCF diets lower average blood pressures by 10 percent. This reduction may be related to increased fecal electrolyte excretion or reductions in the antinatriuretic effects of insulin.

Hypoglycemia. High fiber diets restricted in simple sugar content correct reactive hypoglycemia of the alimentary or diabetic type. These diets alleviate symptoms and prevent chemical hypoglycemia.

Plant fiber intake, thus, have important benefits for selected patients with metabolic disorders. The effects of these diets are well described and confirmed throughout the world. The mechanisms responsible for these effects, however, have not been delineated. The long-term effects of fiber intake on mineral balance have not been determined. Collaborative studies are in progress to address some of these major questions.

JAMES W. ANDERSON, M.D.
Chief, Medical Service
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Bronx, New York

(Hematology & Nutrition and Hematopathology Laboratories)

By

Neville Colman, M.D.

Medical Center

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Veterans Administration

In Reply Refer To:

Hematology & Nutrition and Hematopathology Laboratories.

The research of our laboratories primarily involves studies of hematologic nutrition, particularly that affecting folate and vitamin B_{12} status, with respect to the food sources, absorption, transport and utilization of these vitamins and of their binding proteins.

1. Effect of milk proteins on folate absorption

This study is based on our data indicating that folate uptake by isolated rat gut cells is enhanced up to 20-fold by binding to proteins from either liquid or powdered milks, perhaps of importance in infants with marginal folate nutrition. We have partially characterized the milk factor which enhances folate uptake by intestinal cells, have developed conditions which allow folate uptake to be enhanced up to 20-fold with human milk and 22-fold with bovine milk, have found little damage by pasteurization (with folate binding capacity 72-100% that of raw milk and uptake enhanced 68-93% that of raw milk); similarly, "ultra-high temperature" (UHT) treatment of milk did not significantly damage the folate-uptake-enhancing ability. Folate uptake was enhanced by milk with folate binders previously saturated, indicating that enhancement was either dependent on factors other than binder, or that binder releases and rebinds folate. The uptake of free folic acid by gut cells occurs via a similar pathway but occurs at a slower rate and has a lower maximum; the ligand-receptor interaction showed positive cooperativity and saturability, and about two-thirds of the folate adsorbed to the gut cell surface was internalized into the cell when the steady state is reached within one hour of commencement of incubation. We were able to concentrate the folate-uptake-enhancer in milk by acetone precipitation and rotary evaporation, which removed 80% of the dry weight and 50% of the folate binding capacity without damaging the folate enhancing ability of the product.

The current studies are aimed at characterizing this uptake process and determining its clinical significance. Cells which have taken up folate from milk have been compared with those exposed to free folate solutions, with respect to subcellular localization and cellular metabolism of folates. The effect of milk processing on the proteins involved in the process have been examined, focusing on the possible effect of pasteurization on proteins involved in folate uptake. Animal studies are now underway to determine the clinical impact of milk on folate absorption by *in vivo* assessment.

To determine changes in milk factors affecting infant folate nutrition, human milk samples are being assessed on a longitudinal basis from the beginning of lactation for six months or until a mixed diet is introduced.

2. Folate deficiency in the elderly

Studies are underway to elucidate the mechanism for frequent folate deficiency in the elderly, which has been described by a number of groups including our own. In one set of studies, healthy institutionalized and free living subjects over the age of 65 are compared with those under 35 with respect to dietary intake of folate, and other factors known to have secondary effects on folate metabolism, such as zinc. Concurrent dietary histories are taken to determine whether these can be linked to objective evidence of dietary insufficiency.

In separate studies, possible absorptive defects in the elderly are being investigated by intestinal perfusion of different folates in subjects over 65, with the results to be compared with data previously obtained in younger subjects.

3. Investigation of congenital folate malabsorption. We have studied several subjects with this rare disorder, in which patients present at 2-3 months of age with severe megaloblastic anemia and have varying degrees of permanent mental retardation despite treatment with folic acid. In collaboration with the pediatric hematologists taking care of one patient, we reported our findings that medicinal folic acid (pteroylglutamic acid - oxidized folic acid) when given orally or parenterally was less well transported into spinal fluid than folinic acid given parenterally. Folinic acid treatment apparently improved the patient's status and protected her against the development of mental retardation (in contrast to her sibling who died undiagnosed at the age of 3 months). We are hopeful that the continuation of this new therapy with folinic acid (rather than the old therapy with folic acid) will result in her continued development with no neurologic damage.

4. Vitamin B_{12} radioassay studies. We have continued these studies, particularly around the issues arising from the 1978 report by Kolhouse *et al.* that radioassay of serum vitamin B_{12} level with impure binders sometimes gave normal results in patients who were actually clinically deficient in vitamin B_{12}. We have preliminarily reported that radioassays using pure intrinsic factor occasionally "diagnose" clinical B_{12} deficiency where it does not exist. These data suggest, but do not prove, that humans may use some but not other non-cobalamin corrinoids as if they were B_{12}. Additionally, a patient with clinical B_{12} deficiency and abnormal DNA synthesis both corrected by B_{12} therapy had a microbiologic assay serum B_{12} level of 150 despite a B_{12} level by radioassay with pure intrinsic factor of 0. This suggests some corrinoids which are growth factors for *L. leichmannii* are not growth factors for humans. We are now using five different radioassays plus microbiologic assay with *L. leichmannii* and *E. gracilis* in attempts to determine whether we can find an assay for serum B_{12} levels which uniformly correlates with clinical status with respect to vitamin B_{12}.

5. Abnormal vitamin B_{12} binders in pernicious anemia. We have further characterized an abnormal R binder with high specificity for cobalamin in gastric juice of patients with pernicious anemia which we recently discovered. We demonstrated production of this "cobalamin-specific R binder" from saliva R binder by incubation with pancreatic enzymes. This previously unrecognized cobalamin-specific R binder" indicates the assay for gastric intrinsic factor

from Hall's group in Albany, based on failure of intrinsic factor to bind cobinamide, would erroneously find "intrinsic factor" in the gastric juice of patients who have no intrinsic factor but instead have "cobalamin-specific R binder" which does not bind cobinamide, and could therefore erroneously damage pernicious anemia gastric juice as normal. We are following up these studies to determine whether this newly discovered binder plays a role in the more rapid development of pernicious anemia in patients who lose gastric acid production.

As part of the above studies, we obtained gastric juice from patients with closed-off esophagi and gastrostomies, and determined thereby that the B_{12} binder in gastric juice is almost exclusively intrinsic factor, and that the R binder in gastric juice, previously believed to be made in the stomach, generally comes from saliva and is not made in the stomach. This and the above findings helped us to reconcile the seemingly disparate results of Allen's group in Denver and Toskes' group in Gainesville. Our data suggest their results differ due to their use of different amounts of reactants.

6. Vitamin B_{12} analogues in mammalian tissue. We demonstrated the existence of vitamin B_{12} analogues in human blood cells, liver, and brain. Our finding that B_{12} analogues are only 32% of serum total corrinoids but 60% of dialyzed bile total corrinoids, with 5 individuals having a mean daily bile excretion of 0.89 ug analogue but only 0.65 ug cobalamin, suggests that analogue is delivered to bile preferentially over cobalamin, and that the primary purpose of the system for enterohepatic circulation of vitamin B_{12} may be to filter out the body into the stool potentially noxious cobalamin analogues, which poorly use the intrinsic factor absorption mechanism, while allowing excellent reabsorption of intact cobalamin via that mechanism.

We found stable vitamin B_{12} analogues in the serum of Kalahari Desert bushmen on "natural" diets, indicating that such analogues can arise not only from ingested multivitamin/mineral preparations but also must be absorbed from natural foods and/or intestine bacteria and/or bacterial infections, and/or made by catabolism of vitamin B_{12} within the body.

We found little to no vitamin B_{12} analogue in serum of B_{12}-deficient or vitamin-supplemented fruit bats, confirming Green et al. However, we did find substantial amounts of B_{12} analogue in fruit bat liver, where other workers had not looked for it. Our fruit bat studies are being carried out as part of a project to delineate whether B_{12} analogues play a role in the development of vitamin B_{12} deficiency neurologic damage.

7. Vitamin B_{12} analogues in foods. In studies of vitamin B_{12} analogue content in multivitamin/mineral supplements containing vitamin B_{12} taken by approximately 100 million Americans daily, we found that 10 - 30% of the B_{12} was not B_{12} but analogues. In that study, published in the New England Journal of Medicine (July 22, 1982), we demonstrated that the standard U.S. Pharmacopeia (USP) assay (L. leichmannii) used by all pharmaceutical firms was misleading, since L. leichmannii appeared to grow on some analogues that are not cobalamins. This study suggested that manufacturers should either voluntarily omit vitamin B_{12} from their multivitamin/mineral preparations or indicate on their labeling the presence of vitamin B_{12} analogues. The nature and significance of these analogues is currently being studied, particularly with reference to whether some of them have vitamin B_{12}-like activity for human cells, others have no effect on human cells, and still others may have anti-vitamin activity in human cells.

VA Medical Center

Bronx, New York

(Laboratory of Liver Diseases & Nutrition, and Alcohol Research Center)

By

Charles Lieber, M.D.

Medical Center

130 West Kingsbridge Road
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Veterans Administration

October 17, 1982

In Reply Refer To:

Victor Herbert, M.D.
Chief, Hematology and Nutrition Section
Bronx VA Medical Center
130 West Kingsbridge Road
Bronx, New York 10468

Subj: JSHNR

Dear Dr. Herbert:

The following are ongoing nutritional studies:

1) Drug and Ethanol Induced Alterations of Hepatic Vitamin A and Associated Liver Changes.

The aims of this present study are to determine 1) whether patients who are treated with drugs or consume alcohol have altered hepatic vitamin A levels, 2) whether drugs induce abnormalities of vitamin A metabolism in the liver which might contribute to the lowering of vitamin A, 3) whether there is an associated deleterious effect on the liver. Vitamin A levels are determined in liver biopsies of patients exposed to various drugs or ethanol. Possible relationship between a lowering of hepatic vitamin A and alterations of the Golgi, microtubule network and lysosomes are assessed. The effects of drugs on hepatic vitamin A status is also evaluated in rats. Experimental models are used to determine possible mechanisms whereby drug administration can lower hepatic vitamin A, including bile excretion and increased metabolism of retinoic acid in induced microsomes. The possibility of a selected interaction of retinoic acid with some specific forms of cytochrome P-450 will be evaluated in isolated microsomes and in reconstituted microsomal drug and retinoic acid metabolizing systems. The possible role of lowered hepatic vitamin A in the pathogenesis of liver disorders is being assessed in rats rendered vitamin A deficient.

2) Alteration of Amino Acid and Protein Metabolism in the Alcoholic

Alcoholics were found to have decreased plasma levels of tryptophan, the serotonin precursor, and a decreased ratio of tryptophan over amino acids competing for transport into the brain. Studies conducted in the plasma of rats and baboons with carefully controlled alcohol and dietary intake showed a decrease in the ratio of tryptophan over competing amino acids resulting mostly from increases in valine in the rat and in valine, leucine and isoleucine in the baboon. In the rat this concomitant decrease in brain tryptophan and serotonin were noted. Central serotonin deficiency may contribute to the depressive states frequently seen in alcoholics. We also investigated changes in tryptophan pyrrolase which is considered to be rate limiting for tryptophan catabolism. Rats fed alcohol chronically showed an increased activity of the enzyme in the liver and an increased formation of kynurenine after administration of tryptophan load. This enhanced enzymatic activity may be responsible, at least in part, for the depressed plasma tryptophan levels we observed.

Other plasma amino acid abnormalities are frequently reported in alcoholics with the most common abnormalities being those of depressed branched chain amino acids (BCAA) and increased aromatic amino acids. The depression in (BCAA) is due to multiple factors including portal-systemic shunting, hyperinsulinemia, hyperglucagonemia (all due to advanced liver disease) as well as dietary protein deficiency.

Alpha amino-n-butyric acid is a non-essential amino acid derived primarily from the catabolism of methionine, threonine and serine. We found increased levels due to chronic alcohol consumption may reflect altered glutathione metabolism and lipid peroxidation due to alcohol and may be used empirically as a biochemical marker of heavy drinking.

Theoretical considerations based upon amino acid metabolism in patients with hepatic encephalopathy as well as some limited patient studies have led to the proposal that dietary protein derived from a vegetable source may be better tolerated and more efficacious in such patients. However, studies in normal humans have revealed that vegetable protein is not as nitrogen sparing as animal protein. This prompted us to study the effects of vegetable and animal protein sources in patients with hepatic encephalopathy with respect to mental status, nitrogen balance and plasma amino acids under metabolic ward conditions. No significant differences with respect to any of the parameters studied were observed in relationship to the source of dietary protein but compliance to the regime was much more difficult with the vegetable protein diet.

3) Future Studies on the Fetal Alcohol Syndrome and Pancreatic Disorders

We intend to study the Fetal Alcohol Syndrome (FAS), the leading preventable cause of birth defects and mental retardation. Our studies will focus on ethanol-nutrient interactions and novel mechanisms for teratogenesis and growth failure.

Thus far, no complete FAS model exists in the rat. Development of a complete, reliable, reproducible rat model would be advantageous for further studies in this field. The impact of ethanol, with or without nutritional deficiencies (protein, zinc, vitamin A, thiamine and folate) will be assessed with regard to fetal growth and organ development. In an attenpt to establish whether or not a safe lower limit of alcohol consumption during pregnancy exists we will carry out a dose response study using: a) a dose resulting in blood alcohol levels above those considered legally intoxicating, and b) a dose causing blood alcohol levels below the legal intoxication limit, each with and without nutritional deficiencies.

Another goal of the proposed research is that we also plan to clarify the role of nutrition in the pathogenesis of alcoholic pancreatitis. Previous studies of nutritional patterns in patients with alcoholic pancreatitis have yielded conflicting results. European alcoholics with pancreatitis are reported to consume more protein and fat than age-matched controls. However, Americans with alcoholic pancreatitis are reported to consume less of these nutrients than age or income-matched controls. Thus it appears that while malnutrition is not an absolute prerequisite for the development of alcoholic

pancreatitis, nutrient deficiencies may enhance the likelihood of pancreatitis in some alcoholics. Studies in animals have shown that protein deficiency has deleterious effects on pancreatic structure and function and that these actions can be reversed by the essential amino acid methionine. Since ethanol alters the uptake and disposition of methionine, it is proposed that methionine deficiency may, at least in part, mediate the toxic effects of ethanol on the pancreas.

The specific aims of the research project are the following:

1) To assess the effects of chronic ethanol administration on the rat pancreas under conditions of suboptimal nutrition (protein and methionine).

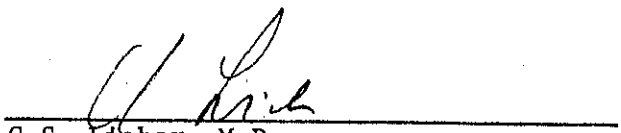
2) To define the relationship between nutritional status and pancreatic exocrine function in asymptomatic human alcoholics.

3) To identify alcoholics at high risk for the development of pancreatitis by the prospective, longitudinal assessment of nutritional status and pancreatic function.

4) Liquid Diet Alcohol Feeding Technique

Many of the ongoing and planned studies are made possible by the application of the feeding of alcohol as part of a total liquid diet.

The technique of feeding ethanol as part of a totally liquid diet was invented by us two decades ago. This technique results in much higher ethanol intake than with conventional procedures. As a consequence, various complications observed in alcoholics were reproduced in animal models, including fatty liver, hyperlipemia, various metabolic and endocrine disorders, tolerance to ethanol and other drugs, physical dependence and withdrawal, the fetal alcohol syndrome and, in the baboon, liver fibrosis and cirrhosis. Variations of the liquid diet formulation are being compared and three standarized basic formulas are being proposed for the rat: A) a regular diet, comparable to the diet previously referred to as the "Lieber-DeCarli Formula" and suitable for most experimental applications particularly those intended to mimic the clinical situation in which the various effects of alcohol occur in the setting of liver changes characterized by a fatty liver B) a low fat diet comparable in all respects to the preceding diet but with a lower fat content, intended to minimize the hepatic changes and C) a high protein formula particularly useful in those circumstances in which oversupply of dietary protein might be recommended (i.e., pregnancy and lactation).



C.S. Lieber, M.D.
Chief, Laboratory of Liver Disease & Nutrition and
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VA Medical Center

Little Rock, Arkansas

By

David Lipschitz, M.D.

Nutrition Research at the Little Rock VA Hospital. D. A. Lipschitz.

Our program primarily studies nutritional aspects of the aging process. Particular attention is foccussed on the development of appropriate standards for nutritional assessment of the elderly, documentation of the prevalence and severity of protein calorie malnutrition in homebased, institutionalized and ill elderly, the reversibility of protein calorie malnutrition by appropriate nutritional intervention and finally the interrelationship between nutrition, age and host defense.

1. Nutritional Assessment of the Elderly.

A large number of nutritional assessment measurements are related directly to height. Examples include the calculation of ideal body weight for height and the determination of the creatinine height index. A reduction in height occurs with aging which creates an additional variable in the development of appropriate standards for the elderly. We therefore examined the use of arm length measurements as an alternative to height in nutritional assessment (J.P.E.N. 6:226-229, 1982). Long bone measurements were determined in 100 young and 62 aged but healthy individuals. A highly significant correlation between height and total arm length was found. As is shown in fig. 2 compared to young subjects arm measurements for the elderly are shifted significantly upwards demonstrating a reduction in height not paralleled by decreases in arm length. This work confirms the previous observation that while height decreases with age arm length remains constant. For this reason we believe that in the development of the standards for the elderly arm length will provide a more accurate reflection of stature than does height.

In a second study the effect of age and sex on the routinely employed measurements used to assess the nutritional status of hospitalized patients were studied (Am. J. Clin. Nutr. 36:340-349, 1982). The results may be summarized as follows:

1. Young control subjects frequently had mean values for the nutritional measurements that were greater than the accepted standards.

2. In young females no significant differences between control and malnourished groups were found in percent ideal body weight (%IBW), triceps skin fold thickness (TSF) and arm muscle circumference (AMC). Although these measurements were significantly lower in malnourished young males than the young male controls considerable overlap between the 2 groups markedly limited the usefulness of the determinations.

3. A reduced creatinine height index (CHI) was a better predictor of decreased lean body mass in young males than in young females. Relating creatinine excretion to total arm length (CTAL) was equally as good a predictor of reduction in muscle mass in males and was significantly better at detecting decreases in young females.

4. In healthy elderly males and females CHI and CTAL were significantly lower than their corresponding young control groups. In general wide overlaps between well and malnourished groups markedly decreased the value of CHI as a nutritional assessment parameter in the elderly. CTAL was a better predictor

than CHI or PCM in elderly males if a lower limit of normal for CTAL was used for the controls. In elderly females CTAL and CHI measurements were virtually identical in both control and malnourished groups and neither method of expression of creatinine excretion was of value in predicting PCM.

5. A high degree of overlap between well and malnourished elderly groups markedly limited the value of %IBW and AMC.

6. TSF was of limited value in predicting PCM in elderly males but was a much better predictor of PCM in elderly females.

7. The hemoglobin and hematocrit only delineated malnourished from control groups in the elderly if a lower limit of normal was used for the controls (12 g/dl for males; 10 g/dl for females).

8. In healthy elderly females the TIBC was significantly lower than in healthy young females. This is due to the higher tissue iron stores that is found in older than in young females and does not reflect differences in nutritional status.

9. The best predictor of malnutrition in any age group was the serum albumin. In both young and old healthy subjects a value below 4.0 gm/dl was extremely unusual and no overlap occurred between any of the well and malnourished groups.

The above observations highlight the importance of considering age when interpreting nutritional assessment measurements. The results also indicate a great need for suitable standards for the elderly.

Based upon these results and difficulty obtaining accurate urine collections we believe that the most appropriate criteria for diagnosis of PCM in elderly are:

a) A history of recent and significant weight loss.

b) A serum albumin <3.5 g/dl. Provided there is no evidence of excessive protein loss and liver function is normal.

c) Features that are usually present but are less definitive evidence of PCM include:

   i) TIBC <250 µg/dl

   ii) Anergy (failure to develop induration at 24 or 48 hours to a battery of 5 skin test applied intradermally).

   iii) Lymphocytopenia

   iv) Anemia (Hb <12 gm/dl in males; <10 g/dl in females)

Nutritional Support of the Elderly..

Nutritional support of elderly subjects with severe protein calorie malnutrition (PCM) has been studied. Extensive experience in the diagnosis of the management of severe PCM in the elderly has been obtained. We have demonstrated

that primary PCM in hospitalized patients is quite frequent. Subjects present to hospital with confusion and infection. Diagnosis of PCM is frequently missed while attention is focussed on the overt reason for hospitalization. We have recently shown that marked improvement in nutritional status can occur with enteral hyperalimentation. In addition to weight gain, significant increases in serum albumin and TIBC are noted. Of importance is the fact that hemoglobin improves, the lymphocyte count invariably rises and anergy is corrected in 80% of subjects followed for a six week period. Our studies indicate that PCM in the elderly is correctable. Furthermore the fact that host defense parameters that are usually ascribed to the aging process are substantially improved by appropriate nutritional support suggests strongly that nutritional status may play a role in these abnormalities.

Nutritional Evaluation and Support of Indigent Homebound Elderly Participating in a "Meal on Wheels" Program.

A complete nutritional evaluation of 65 indigent elderly subjects participating in the "meal on wheels program" has been obtained. After suitable informed consent a history and physical examination was performed. Dietary history was taken on multiple days by the recall technique and blood was drawn for a complete hematologic, nutritional and immune evaluation. In addition a battery of intradermal skin tests were applied and induration was read at 24 and 48 hours. It was hoped to obtain 24 hour urine collections for urinary nitrogen and creatinine but in the home setting and in this population this was found to be impossible.

Few subjects had serum albumin values less than 4.0 g/dl and 90% had values greater than 3.5 g/dl. Many did have other evidence suggestive of PCM. Thirty-five percent had a dietary intake which was less than 70% of the recommended daily allowances for protein and calories. Anergy and lymphocytopenia was present in 45% of subjects and the TIBC was reduced in 35%. Anemia was present in 20% of the males and 16% of the females. Careful evaluation revealed that iron deficiency, folate deficiency or chronic disease was not the etiology of the anemia in the majority. In order to confirm the absence of iron deficiency anemia subjects were given a 1 month trial of therapeutic iron and hemoglobin measurement again determined. Only 1 of the 23 subjects who received oral iron showed a significant increase in the hemoglobin measurement.

From this group of 65 subjects 12 have been selected based upon a high risk of the presence of PCM. The subjects were monitored for a 3 week control period during which time they were seen at least 3 times weekly. After obtaining baseline data they were provided with cans of commercially available polymeric dietary supplement (Ensure plus) of varying flavors and instructed to attempt to drink 1 can containing 350 Kcal in the midmorning, midafternoon and late evening. The delivered meal was usually received at lunch time. A significant increase in total caloric intake could be clearly documented in all patients studied. The amount consumed voluntarily remained constant and an additional 30-60% in total calories was derived from the use of supplement. Increase in total caloric intake could be maintained for at least a 16 week period. Of the 12 subjects examined significant increase in weight (greater than 2 Kg) was seen in 7. The distribution of weight gain as water, lean body mass or fat could not be determined. In addition to subjective improvement marked improvement in some nutritional measurements were noted. A modest increase in serum albumin occurred and a highly significant elevation in circulating TBIC was seen. Highly significant

elevations in red cell and serum folate were noted and leukocyte ascorbic acid levels markedly increased. In contrast no increase in circulating zinc and copper levels occurred and immunologic function did not improve. Our experience and that of others indicate many apparently malnourished subjects fail to gain weight. Possibilites include:

1. The subjects are not malnourished. Like younger well nourished subjects weight increase may not parallel calorie intake. Increased food may be dissipated by increased activity or increased thermogenesis both basally and following meals. It must be emphasized that many subjects who fail to gain weight have strong evidence of PCM.

2. Food absorption and utilization may be abnormal.

Based on the data obtained to date a study is now underway in which the effect of food supplementation on mildly nourished elderly individuals is being examined. Based upon appropriate criteria moderately or severely malnourished elderly subjects are admitted to research beds on the GRECC (Geriatric Research Education and Clinical Care) Unit of the Little Rock VA Hospital. Basal nutritional, body composition, calorimetric and nitrogen balance studies are being performed. Metabolic and physiologic response to significant increase in food intake is being monitored by accurate documentation of calorie counts, changes in weight, anthropometric measurements and radiographic and radioisotopic determinations of body composition. In addition changes in daily energy balance, resting energy expenditure and thermogenesis following a meal is being examined. These studies will provide a rationale approach to the nutritional support of elderly individuals.

Hematopoiesis and Age.

Ongoing studies have demonstrated that anemia is frequent in the elderly. A careful examination has revealed that the etiology is usually not obvious and quantitation of hematopoietic precursors have demonstrated that it is associated with an overall reduction in hematopoiesis caused by a decrease in hematopoietic stem cell reserve. Although the abnormality may be related to the aging process a yet to be defined, potentially reversible abnormality may be present. We have already shown that the hematopoietic profile of subjects with severe PCM is identical to that noted in aged individuals with unexplained anemia. Furthermore intensive nutritional support appears to return hematopoietic and stem cell number to normal. This strongly suggests that nutritional status may contribute to the defect. In order to examine this problem in greater detail multivariant analysis is being performed on data obtained in a large nutritional survey of the elderly in the greater Little Rock area. These studies indicate that age does not appear to be a variable affecting hemoglobin and hematocrit levels in the elderly. The major factor associated with low hemoglobin levels are serum albumin, TIBC and serum copper. These biochemical measurements which reflect nutritional status provide further evidence to support that nutrition plays a role in reduced hematopoiesis seen with age.

The role of nutrition in the aging process is also being examined using in vitro culture techniques. We have shown that nutrient requirements of long term marrow culture in vitro varies inversely with the age of the donor and of the culture. The specific nutrients determining culture survival is being investigated.

VA Medical Center

Nashville, Tennessee

By

Conrad Wagner, Ph.D.

VA Hospital - Nashville

This hospital has no independently supported human nutrition research unit as such. All the nutritionally related research is supported by individual merit review (VA) or by individual research grants from the NIH or from drug companies. In addition, the presence of a CNRU at Vanderbilt has provided a focus for coordinating a good deal of the interest in human nutrition. A metabolic assessment laboratory supported by the CNRU serves as a resource for some of our studies.

The studies may be divided into those which are either basic or clinical.

I. Basic Studies.

A. Dr. Conrad Wagner: Studies on the Cellular Folate Binding Proteins.

Two major folate binding proteins have been discovered in rat liver mitochondria. They have been purified to homogeneity and characterized. The major folate binding protein in the liver cytosol has properties which suggest it may be involved in the storage of folate. The two folate binding proteins in mitochondria also have been purified to homogeneity and shown to be enzymes involved in the turnover of choline. They function in the oxidative demethylation of dimethylglycine and sarcosine to form glycine in the mitochondria. The tetrahydrolate bound by the enzymes serves to scavenge free formaldehyde which would otherwise be produced.

Other studies involve folate transport into the liver. Isolated hepatocytes have been used to identify specific carriers for 5-methyltetrahydrofolate and methotrexate. The uptake of 5-methyltetrahydrofolate by the liver is an energy dependent, active process. This process can be stimulated by conditions which decrease the redox potential of the system. Thus, uptake is more rapid at low O_2 tensions. This is significant because alcohol ingestion results in decreased redox potential in the cell and also causes more rapid uptake of 5-methyltetrahydrofolate by liver cells.

B. Dr. Donald Horne: Studies on Folate Metabolism.

The enterohepatic circulation of folate has been investigated. Rats secrete a significant level of folate monoglutamates in the bile. Bile contains conjugase activity which has two pH optima; 4.5 - 5.0 and 6.7 - 7.5 while rat serum conjugase has an optimum of 6.2 - 7.5. Although biliary conjugase is active, the amount of activity is probably not great enough to contribute significantly to polyglutamate hydrolysis in the intestine.

New separation methods for identification of the various folate monoglutamate derivatives have been developed using a combination of HPLC chromatography followed by microbiologic assay. The microbiologic assay uses L. casei as inoculum stored in glycerol at -20° to obtain reproducible growth curves without needing freshly grown cells each day.

This method permits the rapid analysis of dihydro-, tetrahydro-5-methyl-tetrahydro-,5-formyltetrahydro-10-formyltetrahydro-, and 5,10-methylenetetrahydrofolate derivatives in normal tissue. Studies are now planned to examine the effects of ethanol, folate and B_{12} deficiency upon the distribution of these folate derivatives in animal and human tissue.

C. Dr. Laken Warnock: Studies on Thiamin Metabolism.

Two studies are currently being done on Thiamin (Vitamin B_1). (1) recent studies have indicated that therapeutic doses of this vitamin prevents lead poisoning in animals and suggests that this naturally occurring compound may have potential therapeutic value in the treatment of lead poisoning in both humans and livestock. The mechanism by which this action occurs is not known. Investigations of this phenomenon are being made in laboratory animals under controlled conditions both for the prevention of and treatment of lead poisoning to ascertain the physiological mechanism which takes place. Since there are no known toxic or allergenic effects of thiamin, use of such a compound as a therapeutic agent would indeed by desirable in the treatment of lead poisoning.

Secondly, recent reports have shown the existence of a genetic abnormality in the thiamin requiring enzyme, transketolase, in patients with Wernicke-Korsakoff Disease. The abnormaility of this enzyme appears to diminish the binding of thiamin pyrophosphate to the apoenzyme. Thus these individuals have a much higher requirement for thiamin than normal controls, and in times of stress, such as alcoholism, liver, and kidney diseases, a neuropathy similar to that observed in thiamin deficiency results. The enzyme is found in significant quantities in the erythrocyte. Dr. Warnock has successfully isolated this enzyme from human erythrocytes and is studying its characteristics. Future isolation from erythrocytes of Wernicke-Korsakoff patients will permit comparative analysis to ascertain where and how the abnormality occurs. Full characterization of both normal and abnormal enzyme would permit the development of methodology to identify those individuals in whom this abnormality is manifest.

II. Clinical Studies.

A. Dr. Ronald Gates and Dr. Lloyd King: Vitamin A Binding Proteins in Human Skin Tumors.

Currently there is great interest in vitamin A as an agent for preventing cancer, since the vitamin is required to maintain normal differentiation in epithelial tissue. The most likely mechanism of action for vitamin A is suggested by how steroid hormones work, i.e., the vitamin, when complexed with a cytoplasmic binding protein, affects nuclear transcription. Indeed two cytoplasmic binding proteins for vitamin A (one for retinol and one for retinoic acid) have been found in many tissues and their binding affinities for retinoid analogues [illegible] with the biological potency of the analogue. The anti- [illegible] of vitamin A is probably mechanistically related [illegible] some tumors, including human basal cell carcinomas, [illegible]d with the vitamin. Therefore, these investigators [illegible]omparing the amounts of cytoplasmic retinoid binding [illegible] types of human skin tumors and in adjacent normal

skin. This information is being correlated with pertinent clinical data (patient's age, tumor location and type, invasiveness and recurrence). While this study is just beginning, it was found that basal cell carcinomas have 2 to 3 times as much retinoid binding proteins as surrounding normal tissue. This increase may explain why many basal cell carcinomas regress when treated with topical or oral vitamin A analogues.

B. Dr. Dewey Dunn: Studies on Total Parenteral Nutrition.

All patients receiving TPN in the VA Hospital are monitored by a Nutrition Support Team. Rounds are made weekly by Dr. Dunn (Gastroenterology), Dr. Meng (Physiology), Dr. Blouin (Surgery), Dr. Borum (Biochemistry), Dr. Sullivan (Medicine) Miss Butler (Dietetics) and Miss Basel (Nursing). Patients are monitored for essential fatty acid deficiency and are treated when necessary with appropriate intravenous fat preparations.

C. Dr. Patrick O'Leary and Dr. Gayle Blouin:

1) Nutritional Assessment of VA Patients.

A general assessment of the nutritional status of 1225 successive patients admitted to the Nashville VA Medical Center was carried out. This was then compared with the hospital course of these patients. Preliminary data suggests that the serum albumin levels obtained on admission are a good predictive indicator of the subsequent development of complications. In addition, there appears to be a positive correlation between serum albumin, anthropometric measurements, delayed hypersensitivity reactions, lymphocyte count and weight loss. Approximately 30% of all patients exhibited an abnormal deficit in at least one nutritional parameter.

2) Nutritional Status of Patients Receiving TPN.

A study has been initiated to determine the effect of TPN upon parameters of nutritional status in VA patients. A total of 108 patients who were treated with TPN have been entered into this study. An initial assessment was made either before or immediately after TPN was started. In each case the following measurements were performed: transferin, vitamin C, folate, vitamin E, vitamin A, glutathione reductase, transketolase, transaminase, plasma amino acids, carnitine, free fatty acids, Zn and Cu. These values have been entered into the CLINFO computer and comparison of these values with a normal population is being carried out. In addition, follow-up analysis have been carried out on 20 individuals at various times following TPN therapy to determine its effectiveness. Preliminary data has shown that individuals with low transferin and low albumins usually have low folates, vitamin E and vitamin A. There is also a tendency for vitamin C levels to be decreased. These data will be analyzed to determine the optimal parameters to be used in evaluation of nutritional status and to learn about the effectiveness of TPN in reversing the laboratory indicators of malnutrition.

AGENCY FOR INTERNATIONAL DEVELOPMENT

AID Nutrition Research Program

Overview

By

Samuel Kahn, Ph.D.

OVERVIEW OF A.I.D. NUTRITION RESEARCH PROGRAM

The Foreign Assistance Act (Section 103, Food and Nutrition) states: "in order to alleviate starvation, hunger and malnutrition, and to provide basic services to poor people enhancing their capacity for self-help, the President is authorized to furnish assistance on such terms and conditions as he may determine for agriculture, rural development and nutrition." From this mandate has developed the A.I.D. Food and Nutrition program. The goals of the Agency's nutrition program are two: To enable the developing countries to formulate productive nutrition policies and develop effective programs, and to enable developing countries to maximize the nutritional benefits derived from related government policies and programs such as in agriculture and health. An integral part of the effort to achieve these goals is the Agency's nutrition research program which is focused on: (1) providing more effective programs to combat malnutrition in developing countries by improving the knowledge base needed to analyze the causes of malnutrition, and (2) developing or improving methods and technologies useful in operational programs. Though limited in financial and staff resources for nutrition research, A.I.D. supports a number of carefully selected nutrition research activities that aim at developing new and improved methods or directly applicable key information to combat malnutrition in developing countries. All A.I.D. research is conducted extramurally.

Currently, A.I.D. supports research in the three major categories outlined in the JSHNR's definition of human nutrition research, they being (I) biomedical and behavioral sciences, (II) food sciences and (III) nutrition education. In addition, A.I.D. supports research to study the effect of governmental policy on food consumption and nutrition. Specifically, research is funded to study the effects of both governmental economic policies and agricultural policy choices on people's food consumption patterns and nutrient intake.

A.I.D.'s nutrition research program in education addresses improving the effectiveness of nutrition education efforts directed toward the populations of developing countries. For example, projects have been initiated in the use of mass media techniques for nutrition education; the use of community participation approach to the planning and implementation of nutrition education projects; the use of social marketing techniques to sell basic nutritional concepts.

In the area of biomedicine and behavior, A.I.D. funds and collaborates with CDC in developing and testing modified survey methods for assessing nutritional status and dietary intake. Through a cooperative agreement arrangement with Cornell University, the Agency supports research in the development of appropriate nutrition surveillance methods. This work is conducted in close collaboration with U.N. agencies, especially as they relate to infant morbidity and death. A major research activity is the Agency's project on marginal food intake and its effect on physiological and behavioral function. This activity was initiated at the end of FY '81 as a Collaborative Research Support Program (CRSP) under the Title XII of the Foreign Assistance Act. The principal management entity is the University of California, Berkeley. Field research under the CRSP is being conducted in Mexico, Egypt and Kenya.

The A.I.D. food science program includes research in the fabrication of new low-cost foods, principally for use as weaning foods. Related to this effort, is the research carried out at national and international agricultural centers to develop new varieties of cereals and legumes. Currently, A.I.D. supports two clinical assay laboratories (one each in Peru and the Philippines) which evaluate, in humans, the nutritive merit and safety of these foods. Such food commodities as blended foods (corn-soy-milk, and wheat-soy blend) legumes (soy, mungbean, black bean, etc.) and cereals (wheat, sorghum, corn, rice, etc.) have been tested in this system.

In 1974, former Secretary of State, Henry Kissinger, at the World Food Conference in Rome, committed the United States to combatting both vitamin A deficiency and iron deficiency anemia. A.I.D. was given the responsibility to carry out this task. Two large A.I.D. programs currently focus on combatting these two major worldwide nutritional deficiencies. Significant parts of each program are their research components. For example, major field studies have been conducted in the Philippines and Indonesia on the fortification of monosodium glutamate (MSG) with vitamin A, while the fortification of sugar with either iron EDTA (ethylene diamine tetra acetate) or vitamin A have been studied in Guatemala. More basic research has been supported in studying the effects of iron deficiency on functional impairment, and in determining the etiology and symptomatic sequencing of vitamin A deficiency's pathology.

A.I.D. has organized and funds an international consultative group as part of each program, The International Nutritional Anemia Consultative Group (INACG), and the International Vitamin A Consultative Group (IVACG). Each comprises bilateral donor groups, like A.I.D., and multilateral agencies such as W.H.O., UNICEF, FAO, plus selected world experts and representatives from developing and developed country governments. Both groups function as forums by which each member agency and country becomes aware of what the others are doing to control the specific nutritional deficiency of interest, vitamin A or iron, so that worldwide research and operational efforts can be planned to compliment one another. Both the INACG and IVACG also advise and assist governments in addressing the problem of nutritional anemia and vitamin A, respectively.

Important to both the vitamin A and iron program areas have been the establishing and support of two international centers, each funded under a cooperative agreement and each given the charge of focussing its talent, experience and resources on one of these problem areas. The International Center for Epidemiologic and Preventative Optholmology (ICEPO), under the direction of Dr. Alfred Sommers, was established in September 1980 at Johns Hopkins University. In the Fall of 1982, the International Center to Control Nutritional Anemia (ICCNA), under the direction of Dr. James Cook, was dedicated at Kansas University Medical Center. A description of each follows.

Samuel G. Kahn, Ph.D.
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Bureau of Science and Technology
A.I.D.

AID International Center for the Control of Nutritional Anemia

By

James D. Cook, M.D.

INTERNATIONAL CENTER FOR THE CONTROL OF NUTRITIONAL ANEMIA

James D. Cook, M.D., Director
Kansas University Medical Center

The International Center for the Control of Nutritional Anemia (ICCNA) was established September 1982, by the Agency for International Development (A.I.D.), for the purpose of: developing theoretical and operational concepts for the design, implementation, management and evaluation of programs to combat nutritional anemia. The ICCNA assists in developing approaches which encourage and support developing country initiatives and identify the most effective use of financial, technical and institutional resources for the prevention of nutritional anemias. The center functions as a resource center for A.I.D. in the area of nutritional anemia with special attention given to iron deficiency anemia. The ICCNA, though just organized, already has begun to provide assistance to countries. Its first activity took place recently in Indonesia where technical assistance was given in setting up hematological, biochemical and radioisotopic laboratory procedures for determining both iron status of populations and the bioavailability of iron from indigenous foodstuffs. Prior to establishing ICCNA, KUMC had assisted the following countries in developing strategies and programs for the control of nutritional anemia: Thailand, Philippines, Guyana, Cameroon, Chile, Egypt, Jamaica and Caribbean area.

Plans call for ICCNA to be a back-up laboratory facility to laboratories in developing countries, particularly since the ICCNA laboratory is a lead laboratory under an international collaborative program to standardize critical iron status procedures and techniques, worldwide. ICCNA will also assist developing countries to combat nutritional anemia, through training programs, problem assessment, strategy planning, intervention development and program evaluation. Areas for specific research attention are: bioavailability of iron compounds and factors which influence food iron availability in humans, determining in ecological and cultural settings the etiology of iron deficiency anemia, improving and developing tests for the determination of iron status, conducting studies that explain behavioral patterns which influence iron supplementation compliance, exploring relationships between iron deficiency and specific physiological and behavioral functions, and development of methods for practicable systems of iron delivery suitable for use in developing countries. It is expected that the ICCNA will play a key role in the worldwide coordination of efforts to combat nutritional anemia, a major world health problem.

AID International Center for Epidemiologic and Preventive Ophthalmology

By

Alfred Sommer, M.D.

INTERNATIONAL CENTER FOR EPIDEMIOLOGIC AND PREVENTATIVE OPHTHALMOLOGY (ICEPO)

Alfred Sommer, M.D., M.H.S., Director
Johns Hopkins University

The International Center for Epidemiologic and Preventive Ophthalmology (ICEPO) was established September 1980, by the Agency for International Development (A.I.D.), for the purpose of: developing theoretical and operational concepts for the design, implementation, management and evaluation of nutritional blindness prevention programs; developing approaches which will encourage and support developing country initiatives; identifying the most effective and efficient use of financial, technical and institutional resources for the prevention of blindness caused by vitamin A deficiency. Essentially, the ICEPO is a resource center for A.I.D., specializing in xerophthalmia control. In addition to support from A.I.D., ICEPO is one of seven international collaborating centers for the prevention of blindness which is sponsored by the World Health Organization.

Currently, ICEPO is providing country program assistance to 11 countries: Indonesia, Tanzania, Malawi, Zambia, India, Bangladesh, Philippines, Nepal, Haiti, Bolivia and Mexico. Assistance is planned for Mali, Upper Volta, Benin, Togo and Senegal. This assistance is both short-term consultant services and in-depth advisory assistance to countries considering on implementing nutritional blindness prevention programs. This may range from a few days consultation regarding very preliminary activities (e.g., is it possible to piggy-back a vitamin A deficiency assessment into an existing survey design?) through long-term involvement in all stages of developing and implementation of intervention programs, including evaluation inter-relation of results and preparation of reports on program impact. Frequently, definition of the best program strategy or intervention approach requires operations research. When this is the case, ICEPO is prepared to be involved, whether solely in an advisory capacity or on a collaborative basis, depending on the situation. This is a two-way street -- the information, experience, and procedures emanating from country activities are channeled by ICEPO directly to other countries, into state-of-the-art documents, into manuals, and through a variety of dissemination channels into the world body of knowledge. The following list illustrates the specific types of project research activities undertaken in country: development of vitamin A deficiency surveillance procedures; developing and testing new recognition procedures; explaining the relationship between measles and xerophthalmia; determining etiology of vitamin A deficiency in different ecological and cultural settings; and conducting operational research toward development of intervention programs. Much of this research is applied or operational. In addition, ICEPO assists in developing country strategy for combatting vitamin A deficiency, designing and implementing a variety of training programs, functioning as a backstop laboratory in histopathology, biochemistry, and other needed techniques, designing data management and processing systems and carrying out general program trouble shooting.

SPECIAL PRESENTATION

The Impact of the Clinical Nutrition Research Unit Program on Medical Education

By

Alfred E. Harper, Ph.D.

THE IMPACT OF THE CLINICAL NUTRITION RESEARCH UNIT PROGRAM ON MEDICAL EDUCATION

Strengthening the environment for education in nutrition in medical schools was one of the objectives established for the Clinical Nutrition Research Unit (CNRU) program. The limited space given to education in nutrition in medical curricula was a concern of the League of Nations Commission on Health during the period between 1935 and 1938. The Commission, in a technical report published at that time, deplored the dearth of education in nutrition in most medical schools. This statement was accompanied by a plea for increased emphasis on rational education in nutrition in medical teaching programs. This plea, and many similar pleas subsequently by others, did not fall on particularly fertile ground. Development of the CNRU program represents the most recent effort to increase awareness of the importance of nutrition as a component of medical education and medical care. The challenge to those who applied for funding under this program was: "To strengthen the training environment in nutrition in order to improve education of medical students, fellows, and house staff." It is, therefore, appropriate to ask, even though the existing CNRU's have been functioning for less than 4 years, what progress has been made in responding to this challenge.

As CNRU's have been established in medical settings where, at least in some departments, nutrition already existed, it is difficult to distinguish clearly between developments in medical education that should be attributed specifically to the presence of a CNRU, and those that were occurring as the result of efforts by faculty who had been working over the years to achieve essentially the same objectives as were proposed for the CNRU's. In order to obtain information that would permit some assessment of the impact of CNRU's on the environment for education in nutrition, each of the CNRU directors was asked to provide a summary of the nutrition program at his institution and to indicate how establishment of a CNRU there contributed to the development of this program. I have used these reports to identify ways in which CNRU's have influenced medical education in nutrition at the different institutions. First, I want to make a few general observations, then I shall summarize some of the specific developments at individual institutions.

The CNRU directors, without exception, agree that the establishment of the Clinical Nutrition Research Unit has, and I quote directly from some of the reports: "strengthened the place of nutrition in the medical curriculum...has given an impetus towards increased consolidation and less fragmentation in the presentation of nutrition knowledge in the curriculum...provided an impetus for expanding nutrition education in the medical school...enriched established nutrition offerings, especially by forging stronger links between the basic and clinical activities in the medical school...upgraded nutrition programs in medical education...improved the environment for nutrition in the medical school itself...and heightened awareness of the importance of nutrition within the medical curriculum." Although these are not quantifiable effects, nonetheless, I think they indicate more about the influence of the CNRU's on medical education in nutrition

than do any of the specific actions reported. Acceptance of nutrition in the medical curriculum on a basis comparable to that of the traditional medical subjects depends on the attitude toward nutrition in medical schools, and on the existence of an environment in which nutrition is considered an important component of medical education.

Our experience at Wisconsin parallels that expressed in the quotations I cited. Awareness of nutrition has increased. There are more requests for presentations of nutrition lectures and seminars in both clinical and pre-clinical courses. Nutrition faculty are asked about the nutrition program more frequently than in the past. Also, opportunities for collaboration in research have arisen more often. There are more requests for nutrition representation in grant applications generated by other faculty and other departments. I sense, from the commentaries of the other principal investigators, that this heightened awareness has been a general phenomenon. It has begun to provide more bridges between basic science and clinical faculty than existed previously. Several directors indicated that collaboration and cooperation among the faculty has increased. This is seen in the development of more joint research projects. This shift in attitude toward nutrition as a medical subject is a major step in ensuring a stable place for nutrition in medical education.

In my comments so far, I have purposefully identified relatively few specific actions at the individual centers because I wanted to emphasize first the similarity of the tone of the responses of the various directors. This approach, I believe, catches best the nature of the general influence of Clinical Nutrition Research Units on the environment for nutrition in medical schools.

The various CNRU directors have also provided information about specific actions that have broadened and strengthened medical education in nutrition. For example, establishment of CNRU's has led to the initiation of new course offerings or expansion of existing offerings in several schools. Expansion of seminar programs seems to have occurred fairly generally throughout the various schools. Strengthened nutrition support services have increased opportunities for students to learn about nutrition problems in patient management; both Dr. Rosenberg and Dr. Winick mentioned this in relation to their units. At least four of the directors reported an increase in nutrition offerings in grand rounds. Development of the Clinical Nutrition Research Unit has also provided opportunities for research projects for house staff and fellows, and so, has expanded this aspect of education in nutrition. Dr. Rosenberg mentioned, particularly, the acceptance of the graduate program in nutrition for physicians which has been instituted recently at the University of Chicago.

There are, nonetheless, substantial differences in the extent to which nutrition is incorporated into the medical curricula at the different centers. It may be of value to indicate some of these, despite the difficulty in identifying what relationship these differences have to the development of the CNRU's.

In Dr. Rosenberg's program at the University of Chicago, nutrition topics are introduced in the medical school curriculum in biochemistry during the first year. This is quite traditional. It is continuing, I think as it should, and is representative of several of the medical curricula reviewed. In Chicago there is a clinical orientation program for the incoming student. This covers topics in organ physiology in relation to metabolism. In the second year, students are introduced in clinical pathophysiology and clinical pharmacology, and in the third year, in medicine, to nutritional aspects of diseases. In the third year also, there are two electives which cover physiology of human nutrition and nutritional pathophysiology. Then, in the fourth year, the students receive further instruction on aspects of disease and disease management which, I assume, is linked closely with clinical activities.

In Dr. Butterworth's program at Alabama, more time is allotted to nutrition in the formal curriculum than in any of the other programs I reviewed. This came about, I understand, partly because there has been a nutrition component in the medical curriculum there for many years, and 5 years ago, during a revision of the curriculum, an opportunity arose to increase the nutrition component still further. They list 52 contact hours in nutrition during the first year, with emphasis on clinical implications of nutrition. Some 20 hours are on topics such as obesity, eating behavior, diabetes, cancer, hypertension, vegetarianism, growth and development, pregnancy, cardiovascular diseases, and dental diseases; 14 hours on basic nutrition, primarily vitamins and minerals; and 18 hours on topics such as malnutrition, nutrition assessment, nutritional therapy, enteral and parenteral feeding; and some coverage of special clinical problems including such topics as renal dialysis. Then, in conjunction with the nutrition support service, a 4-week clinical elective has been developed in the second and third years. This has been a successful and attractive program for medical students with a high proportion of the class applying for about 12 places.

Dr. Feldman's program at Georgia includes 28 lectures on nutrition. A series of objectives and handouts are used to expand these. They have some additional lectures on videotape. They also have clinical nutrition electives for junior and senior students and nutrition clinics that cover patient assessment and include didactic sessions. One or two students a month have the opportunity to participate in this clinic with a nutrition team consisting of a physician, a nurse, and a nutritionist and together with an intern or the house officer in internal medicine. The patients are from nutrition consults from the various hospital services.

Dr. Greene at Vanderbilt reported that their major offering is in the nutritional biochemistry course for first year students with about 32 hours of nutrition instruction, 8 hours of basic nutrition lectures, and then a series of 3-hour discussions and demonstrations with clinical emphasis in which the CNRU faculty are fully involved. In the fourth year, an elective on clinical management is offered which includes about 6 hours of clinical nutrition.

Dr. Rivlin at Memorial Sloan-Kettering in New York, indicated that they have a first year elective in nutrition with about 13 hours divided between basic and clinical aspects; in a required course in the second year about 8 hours are devoted to nutritional topics such as obesity, cancer, aging, and diabetes; then, a 10-hour elective for students who want to study nutritional problems in greater depth.

Dr. Winick stated that, at Columbia Medical Center in New York, their program also starts with a basic introduction to nutrition in the biochemistry course in the first year; following this, a clinical elective in nutrition is offered. A required course in nutrition had been developed previously by the Institute of Nutrition which, he emphasized, has been strengthened by the Clinical Nutrition Research Unit activities, which have been largely in pediatrics.

In our program at the University of Wisconsin-Madison, again emphasis in the first year is on physiological chemistry. Nutritional emphasis in that course is not strong, but students do obtain basic knowledge of vitamins, minerals, intermediary metabolism, and metabolic integration. The second year is organ oriented, but includes 14 hours for nutrition in which topics such as nutrition and the life cycle, fuel homeostasis, hyperlipidemia, drug-nutrient interactions, and nutritional requirements and allowances are discussed. There is a laboratory exercise on dietary histories, food composition, and evaluation of the adequacy of diets. This is often a revelation for the medical student who has heard recommendations for some rather drastic changes in diet without ever thinking much about what this involves for the patient. In the third year, during the clerkship, opportunities are provided for students to interact with patients who are being examined by the nutritional support service. Clinical nutrition rounds and weekly conferences are attended by a number of the students and house staff. For the fourth year, Dr. Shrago and some of the other faculty have developed an elective course entitled "Current Topics in Clinical Nutrition," which is given in both the Spring and Fall and is taken by some graduate students and a number of medical students.

A number of other activities that impinge on nutrition education have also been developed in connection with the CNRU programs. Both Vanderbilt and Georgia, for example, have newsletters. These provide a substantial amount of information about nutrition topics, often on topics of current interest and topics that may be controversial. Dr. Rivlin mentioned that they have prepared a number of information pamphlets on nutrition topics that are distributed to students in certain classes. Noon conferences on nutrition have been organized for the faculty in Georgia. Dr. Rosenberg indicated that they are developing conferences in relation to nutrition activities that include both faculty and students in the planning of research programs. These are representative of the variety of types of activities that have been generated as a result of the establishment of CNRU's.

In conclusion, it is evident that the Clinical Nutrition Research Units have had an impact on medical education at a variety of levels

in the medical schools in which they have been established. The directors agree that the CNRU's have given visibility to nutrition programs, have increased opportunities for participation by medical students and fellows in research projects on nutrition problems, and have increased awareness among the faculty of the importance of nutrition in the management of patients and of the role of nutrition support services. The reports from the CNRU directors indicate uniformly that establishment of CNRU's has strengthened the place of nutrition in the medical curricula of the universities participating in the program. The comments received indicate that there is less fragmentation in the presentation of nutrition knowledge, an impetus for expanding nutrition offerings, an improved environment for nutrition in the medical schools, and a heightened awareness of the importance of nutrition within the medical curriculum.

PLANNING FOR NUTRITION RESEARCH

Dr. Artemis Simopoulos: The whole question of planning is open for discussion; anyone who wishes to make comments is welcome.

Dr. Irwin Rosenberg: I'll start out by unburdening myself of some of my doubts and concerns about this process and then, perhaps, if those can be gotten out of the way, we can go on to some positive developments. While I feel very positively toward the idea of the need for planning in this area, with the kinds of specifications that were made yesterday, I have some real concerns about the contexts in which planning will be done for nutrition research in the absence of a Federal plan for nutrition. If we take seriously the observation that was made yesterday, that Congress is going to support nutrition research because it will lead to developments which better the health and welfare of our population, then that is another way of saying nutrition research is fine, but it has a goal. It is not going to be supported simply for its own sake. If the goal is to improve the nutritional status of the American population and therefore its health and welfare, then it seems to me that the context in which these new observations and this information is going to be used needs to be defined. Most of you would probably agree with me that a coherent, cohesive, national nutrition plan is not easily found. Certainly the priorities of research are going to have to be linked to some extent to the priorities of a national nutrition plan.

I would make the observation that there is no amount of effective research planning that is going to influence political decisions that are made about when to cut funding for the nutrition information service of the USDA, which, in turn, might end up seriously cutting the information gathering aspects of that service about dietary habits and the population. However, if this information gathering is part of a national plan, then its seems to me that such changes would not be made willy-nilly. I simply make the plea that we give some thought to the need for a national nutrition plan, as well as the need for a research plan.

If everyone agrees that we can make a research plan without having a national plan, I would suggest that what we really need is somebody or somebodies to begin to plan for that plan. If we have expertise in this room, it is expertise because we know something about what is going on in nutrition, not what is going on in planning. I would ask, perhaps I should pose this question directly to Dr. Simopoulos, is there the capability within the Subcommittee to take on the responsibility and the expense involved in evolving a national plan in consultation with the kinds of elements that we have here in this room for the last couple of days, or if not, where should that responsibility fall? Should it be perhaps, in part, contracted out to other think tanks, possibly FASEB, the Food and Nutrition Board, and so forth? I really would like to hear some thoughts, not about general concepts of planning, but where can the actual job of producing a plan for a plan be created.

Dr. Artemis Simopoulos: Thank you, Dr. Rosenberg, for the very thoughtful comments; I probably agree with everything you have said. The Joint Subcommittee could attempt to develop at least a skeleton of a plan--remember, we are not just isolated individuals, we represent agencies. The agencies themselves have advisory committees, councils, programs, and staff. So, although we may be just a total of five or six people at the table, we are indeed going to get information and input from our agencies, and certainly the agencies get input from the scientific community. Having put a skeleton of a plan together, this Subcommittee will have to get additional input from the scientific community, and I would hope, from Congressional staff, from private foundations, and other groups that are interested in planning for nutrition research. But, to begin with, we have to get started here, develop the skeleton, and then progress from there. This is the way I see it right now, but I think all other members of the Subcommittee might wish to comment on it.

Dr. Mary Carter: What I hear you saying, sir, is that you feel we should have a national plan for nutrition before we can develop a research plan for nutrition. Is that what I hear you saying?

Dr. Irwin Rosenberg: No. Although it would help, I'm not saying we should wait for that.

Dr. Mary Carter: I would like to switch to my own terminology for communicating this type of thing. I think that we should have in the human nutrition area a goal, for example, the health of our citizens in this country. Everything that we do with regard to planning should be targeted toward this goal whether it's some nutritional status of the people of this country or the world. One of the things in my brief experience in this general area of R&D management is that sometimes one of the best ways to start targeting what your goal should be is to start at the ground up. In other words, get the performers in the arena, the people who are concerned with this whole area of nutrition and health, to help you in the formulating of your goal. In that way we can be sure that we are hearing from all the participants across the country, whether they are the performers of the research, the users of the information, or the ones who benefit from the information. This approach is one that we could think about trying in the coming year.

It is true, as Dr. Simopoulos said, and I concur completely, that the various Departments in Government, and the agencies within those Departments, do have their own planning tools and can also make a contribution. All this would need to be meshed together. Of course I could also visualize, Dr. Simopoulos, that perhaps some of these activities could be coordinated by the Joint Subcommittee on Human Nutrition Research.

I would like to see a broad range of participants help us set a goal that meets everyone's needs, including the Congress and the Executive Branch of the Government; but we must all do this together.

Lt. Col. David Schnakenberg: I tend to agree with you, Dr. Carter; what you propose is in a broader overview, not unlike how the Department of Defense begins to build its research plan. We start, in our terminology, by going to the user. If it is in a medical area we go to our Health Services Command, who looks at the issues relative to health care delivery. We also receive input from those who are responsible for our combat troops and what their needs are now and in the future. Thus, we have the participation of the expertise from the biological sciences along with the line officers in terms of developing what the needs are. We call it "Mission Area Analysis." This analysis begins to flow up through the system and ultimately comes to someone to make the hard decisions based on priorities and available funding. I think that process is what you are referring to here. Such a process needs a focal point to get the process started and to "keep book." Possibly the Joint Subcommittee should do that, I do not know who else would. That role would be appropriate for the Subcommittee, since it would be far too presumptuous to assume that half a dozen people that meet every couple of months would have the breadth of background to undertake the task alone.

Dr. Artemis Simopoulos: Anyone else?

Dr. Samuel Kahn: Let me just speak from my own experience. I know that our agency has a written policy and a formulated strategy with regard to nutrition. I am sure that most other agencies have, or should have, a formulated policy and a strategy, the two being different. I think I would use those terms, "policy" and "strategy," rather than the general term "plan," since they mean specific things. If we knew exactly what the nutrition policy and strategy are for different agencies we could do a better job of putting it all together and trying to formulate a unified nutrition policy and strategy for Government. I would suggest that we, as the Subcommittee, could start pulling these things together by determining what each specific agency has in terms of written nutrition policy and strategy.

Dr. Mary Carter: Sam, what would we do once we got such documents together? We don't represent all the human nutrition research that's going on in the country.

Dr. Samuel Kahn: No, but we represent the principal agencies in the Government. I thought that what we are talking about here, today and yesterday, is what the different agencies are doing in-house and extramurally, and to see if we can put together a unified order of activities. I think we can do that.

Dr. Victor Herbert: On this question of a national nutrition policy, one might in a sense conceive that there is such a policy, and that the Joint Subcommittee elucidated it. The reason I say that can be found in the American Journal of Clinical Nutrition, May 1981 Supplement, copies of which are available outside. That supplement is a report from the Joint Subcommittee in which critical issues in human nutrition research and research training in the 80's are identified and conclusions and recommendations are made which really do constitute a fairly well articulated nutrition research program for the country.

All the ten Federal agencies signed off in agreement on these as nutrition goals for the country. Now, just because it was the Federal agencies who signed off on it and the Congress did not officially pass it as an Act does not make it any the less operative. I am sure it is operative in the Veterans Administration.

Dr. Irwin Rosenberg: In practical terms, would it not be important that a carefully structured statement appear in a form available for use.

Dr. Victor Herbert: I would agree with that. I think it would be nice if Congress were to convene the equivalent of a Congressional workshop, which is something they do regularly, to take up a major subject like the provision of nutrition information to the public; they could similarly take up the subject of creating nutrition goals for the nation and I think they would very likely articulate similar goals to the ones in the JSHNR report. The VA, for example, articulated nine specific areas of human health research in which they felt the VA had particular interest. Five of these were in nutrition. You heard this morning about part of our programs in two of those areas: nutrition with respect to alcoholism, and nutrition with respect to aging.

Dr. Samuel Kahn: I understand fully why people referred to our national goals, but you have to realize that the nutrition research that was presented in the last two days extends further than national goals. I would like not to be excluded from that. We really should put together a policy and strategy which is for nutrition research that covers all nutrition that has to be researched. That extends beyond just the concerns that touch our populations. It includes concerns that may touch other populations. I think we should look at the problem as broadly as possible, and not limit or constrain ourselves just to the problems in this country.

Dr. Victor Herbert: I think the report does do that, Sam.

Dr. Samuel Kahn: I think that report refers to the fact that a report on international nutrition was going to be prepared subsequently, as well as one on nutrition education, so that the report addresses the issue somewhat, but it does not, in itself, cover all the things the JSHNR covered subsequently.

Dr. Artemis Simopoulos: The international report is available outside. I think there were more comments. Dr. Harper and then Dr. Rivlin.

Dr. Alfred Harper: I keep having trouble with the term planning; I am not quite sure what it means. I feel much more comfortable with Dr. Kahn's suggestion that we are really talking about policy and programs; what he calls strategy. I would include in "strategy" the development of programs as well as the objectives of programs. If we do not make this distinction, we get at loggerheads as to whether we are planning for exchanging information, or planning to achieve a specific objective that requires research activities.

Unless we start at the top with a broad view and then narrow down, I think we may find ourselves in a quagmire. The point of planning is to achieve some objective, which is essentially establishment of policy. If the policy is to improve the health of the population, this is one thing; if the policy is to reduce the cost of medical care, that may be quite another. Unless we establish policy and a set of objectives at the outset, planning is likely to be futile. To my mind, the goals that we have discussed become a part of the policy.

I have some concern with the establishment of goals. Sometime back, I recall a set of goals that were called "Objectives for the Nation." In fact, I attended a conference at which some of these were developed (eventually I asked to have my name removed as a participant). They were put in terms like this: reduce obesity by 15% by 1990; reduce serum cholesterol concentration to 190 milligrams per deciliter by 1995. Now these objectives are absolutely unrealistic. To set objectives of this type without any planning and call them goals for a program is not, to my mind, a fruitful type of activity. I would like to see us start with the establishment of a general policy and then identify the important problems that need to be solved. Some of the problems that the Federal agencies must deal with are different from those that are major concerns of individual researchers. After the problems that truly need to be attacked are identified in specific terms, then we can plan programs. We can also plan for the type of information exchange and collaborative efforts that are needed to solve these problems. I feel that we need some clearing of the air if we are to get on the right track.

Dr. Artemis Simopoulos: Thank you, I do not think we are going to respond to all the comments but I think these are very important and we are going to consider them. I would hope that we are not going to repeat mistakes. Dr. Rivlin.

Dr. Richard Rivlin: One of the things that troubles me in hearing this, is that I believe we have to think beyond a plan. Our field is full of decisions that have been made and plans that have been created. It is very important to develop realistic plans, but let us think beyond this, to how such a plan would be implemented. We are all very grateful to Dr. Simopoulos and to all of you for your political activities. Clearly, we have seen one member of Congress who is very supportive of us. But I wonder if we are sufficiently effective or active in the area of public information. After I go to the bookstores and listen to the media and hear all the nonsense that is being promulgated to the public, I wonder if we are sufficiently active politically to make our views known in order for a plan that we develop to be likely to be effected. I think it will be a tragedy if a great effort were made to develop a plan that really did not have a realistic chance of succeeding. I wonder what thoughts are being given to how we may mount a major effort to convince both the public and the Congress, and further down the line many other groups, of the theoretical value and the practical significance of this plan.

Dr. Artemis Simopoulos: Does anyone want to respond to that?

Dr. Victor Herbert: I would just like to put a question to all three of the questioners: Who do you perceive as having the power and authority to implement this proposed national plan and to whom do you suggest we go.

Dr. Alfred Harper: I am concerned first about participation; that is, who is to identify the major problems. I do not see that as just a Government responsibility. It is also a responsibility of the professional community, probably with input from other groups who may not be in the health professions but whose suggestions would need to be reviewed and screened. The place to start, it seems to me, is with a combined Government and professional group.

The only organizations I know of that can institute the types of policies and plans we are discussing are Government agencies. If it is a national responsibility to achieve a certain goal or objective, who besides the Federal government can do that? If we need more wheat, it is the responsibility of the Department of Agriculture to develop methods for increasing wheat production; if we want to reduce the incidence of some common disease, it is the responsibility of the Department of Health and Human Services to develop the strategy for doing that. It seems that simple to me unless, of course, Congress decides that the problems have not been identified properly, the objectives are inappropriate, or the policy does not merit support.

Dr. Artemis Simopoulos: Thank you, Dr. Harper. I believe that Dr. Rosenberg wishes to comment.

Dr. Irwin Rosenberg: What I said before is that I think somebody has to take responsibility for the leadership to create what Dr. Simopoulos referred to earlier as the skeleton of the plan. I think some coordinating body would have to do it, with the appropriate kinds of communications to which Dr. Harper referred. We must recognize that we are talking about policy goals and research goals that become goals toward the implementation of a broader policy. I would not put my faith and trust quite as fully in the interagency mode as would Dr. Harper, and I would recognize that in the final analysis the financial implementation of these matters are going to depend on actions of Congress. Since Congress no longer defers entirely to the agencies in terms of its own sense of planning and technical evaluation, I would wonder whether we might ask someone like Dr. Grace Ostenso what she thinks about the way in which such a plan might interdigitate with the way Congress goes about its business.

Dr. Artemis Simopoulos: Thank you, Dr. Rosenberg. Grace.

Dr. Grace Ostenso: I was invited as an observer and I had hoped to maintain that status but obviously I cannot. I do not know where to begin. I have heard a lot of discussion about terminology, and you have to go through that process. But in the end I would hope that you would develop some kind of mechanism to approach whatever plan, policy, objective, goal or whatever you decide to call what we are talking about. That mechanism should have absolutely nothing to do with nutrition, per se. By that I mean that you may want to use a

tool such as the infrastructure for research in general to delineate what now exists in nutrition research and the critical mass that you need in the future. Things such as: what needs to be done to develop nutrition centers of excellence while maintaining its scientific integrity; what are the needs in nutrition research for a communication network, facilities and equipment, funding sources, academic-industry-government partnerships, manpower and training, journals, a central focus, data bases, data base management. Maybe if you look at it in some way other than research outcomes only, and step back from what we are so close to, it might help the process.

The answer to your question then, is that I do not think you will have any difficulty in getting an arena established within the Congress to listen to whatever you develop and put together. Then, once you've got a mechanism in place for developing an agenda, other things will come into focus and you will begin to separate research priorities from ways to make implementation happen.

In terms of selling the plan, you first have to have a product to sell, both to the Congress and to the public. You may have to have two formats of your plan, one to sell to yourselves as the researchers and an overlay for explaining the value of the plan and nutrition research to the Congress and the lay public. If you can sell the plan, policy, strategy, whatever it is called, to the lay public by enhancing their understanding of the importance of nutrition to their daily lives, then you have sold the Congress. The public is the Congress' constituency.

One other point. Whether you develop a national "plan" or a Federal one, I agree with the concept you have to start somewhere. As Congressman Brown said yesterday, you have to define logical planning units and then find ways to interlock those logical units. Perhaps as a fallout from a Federal plan you will formulate ideas of what ought to be included in a national plan. Planning is circular and should never be carved in stone. If the Federal plan precipitates a national one, great. Once the national one is drafted, the first thing you will have to do, or even before, is to revise the Federal one. In terms of where the activity ought to be centered, there is a National Science and Technology Policy Act which created the Office of Science and Technology Policy of which this Subcommittee is a component. OSTP has not addressed interagency coordination or long-range planning as well as expected when that role was established for them by the 1976 Act. OSTP is limited in resources and in staff, but one of the things they have done quite effectively in other areas is to bring together a broad participatory group. It would seem to me that it would be helpful if a group with broad representation could be established to develop at least a beginning point and demonstrate progress accomplished by the "scientific community," not just the Federal Government. Then you might be able to gain some resources either from within the agencies to contribute to the planning activity, or from some legislative initiative to continue the planning and implementation processes.

Dr. Artemis Simopoulos: Thank you, Dr. Ostenso. Dr. Rivlin, I think Dr. Ostenso more or less answered some of your concerns: the public is very important and should be well informed.

Dr. Irwin Rosenberg: I am delighted to hear that there really are ongoing mechanisms whereby this process can be effective. I still feel that a great responsibility lies with the scientific bodies in nutrition to make their efforts known to the public. For all too long we have been speaking to each other and we have not adequately let the general public know about the advances that have been made, the unanswered questions, where the status of a particular question lies, etc. All too often when the efforts of nutritionists are mentioned in the press, it is usually to underscore the controversies, rather than those broad areas about which we all agree. I would like to see the public better informed about these broad areas of agreement, about accomplishments to date, and goals for the future.

Dr. Artemis Simopoulos: Thank you.

Lt. Col. David Schnakenberg: If I may, Dr. Simopoulos, I would like to follow on that point; I think it is well taken. We are trying to grapple with that within our own agency at the moment, since we are in the process of trying to establish what is the message in terms of nutrition we want to get to our constituency in DOD, not only the active duty member but also his family. We want to try to establish that centrally out of the office of the Surgeons General of the three services, and then be able to disseminate the message through a network, at least within the Army, at each medical activity on every post.

By having a special team of four to five professionals at each medical activity, we will be able to reach out and effectively deliver the basics of the message to at least one sector, the population of two million active duty military plus dependents, a total of around 4 to 5 million people. So we have a community of 4 to 5 million people out here to whom we might be trying to present a message, and we would hope that we could have that be a responsible message and thereby increase the awareness of that constituency. They, in turn, would interact with their Congressmen, if necessary, in supporting further information and further advancement in this area of science.

Dr. Artemis Simopoulos: Thank you, Col. Schnakenberg. Dr. Grundy, you had a comment to make.

Dr. Scott Grundy: Speaking as someone who is not directly in the Federal program at the present time, I think that the Federal agencies involved could perform a leadership role to the rest of the scientific community. Perhaps what is needed is a task force or commission to identify the problems in nutrition which would involve not only Federal agencies but also the rest of the scientific community in putting together a priority list and identifying problems in nutrition for the country. I think such a group would serve not only to focus the attention of the Congress but would also provide lead-

ership for those of us who are attempting to set up programs in nutrition, of which more and more are being set up in medical schools and universities. Frankly, since developing a plan for a nutrition program is new and does not fit into the usual mode of medical schools, it would be extremely important to have leadership and guidance at this point.

Dr. Artemis Simopoulos: Thank you. Any other comments.

Dr. Walter Mertz: I would like to comment on the two questions that were raised yesterday and that are being discussed now: communication and planning. I greatly appreciated this meeting, because I gained a tremendous amount of new information. We actually generated some new ideas, and I am very grateful for this. I see a very great value in the activity of this Subcommittee and I hope that we can continue these meetings. We have had pretty good communications all these years, but I think this formalization of communications is needed and will be very beneficial.

That was the good thing, now comes the bad one. I have an allergy against the term "planning." The three good plans that we have discussed today, the one of the Cancer Institute, the one on vitamin A, and one on iron deficiency, are all well thought out plans for an action program. They are possible only because some scientist in some cubbyhole has first come up with an idea and has solved a problem, at least theoretically, to such a degree that it can now be applied large scale. The whole effort of iron deficiency that Dr. James Cook talked to us about this morning would be impossible had not he and Clem Finch come up with the idea of the non-heme iron pool. If we had an august committee 20 years ago, I guarantee you that if somebody would have brought up this plan for intervention against cancer they would have thrown him out; even 10 years ago nobody would have admitted there was such a possibility. What I am saying then is that the major and primary events in our field in scientific research are new ideas. They are unpredictable where they come from, they cannot be planned. The only thing we can plan is execution and implementation of these ideas. For this reason I am very, very happy that the great majority of the NIH funds goes for individual grants that leave the scientists the opportunity to come up with great ideas. We should, therefore, be very careful when we talk about planning of national policies so that we do not stifle the freedom of scientists who come up with great ideas. These ideas are the only contribution that keep our field alive in the long run.

Dr. Mary Carter: Dr. Mertz, I want to follow up on some of the comments you have made because I think your points are well taken and it seems to me that one of the greatest benefits that has come from these two days together has been the opportunity for people with mutual interests just to get together to talk about these areas or problems or what they are doing. I have wondered where we go from here to continuing this dialogue in order to surface not only just program and problem areas, but also maybe some priorities. I have wondered about the need to identify some program areas within the next 3 to 6 months and if we shouldn't almost do this over again but

in a different fashion. I was thinking of simultaneous workshop groups with actors from all agencies addressing a general program area, talking about the things that need to be done in this area, and then getting back together in planning sessions and some discussions like these so that we can have the performers and the users sharing information and addressing concerns. Perhaps this should be the next action item that the Joint Subcommittee should consider as we try to move together down this road to develop policy and strategies and at the same time begin to develop dialogue and understanding in a broader community. Does anyone care to give some opinions as to what you think we ought to be doing and how we can go about working together.

I see Dr. Iacono back there; don't be hesitant, it is a great opportunity that we have to be together this afternoon.

Dr. James Iacono: I think the comment you have just made and Walter Mertz's comments are very apropos. I came here with great expectations and I was really amazed how much I gained from these meetings despite the fact that no in-depth presentations were made of the Federal nutrition research programs. It seems to me if we are going to get a handle on Federal human nutrition that we need some kind of a meeting or meetings as you have suggested, to give us greater exposition of the various aspects of human nutrition that are under way in the Federal Government. What you have suggested, Dr. Carter, may be a good idea. We should consider broader scale meetings arranged in such a manner that they can be subdivided into various categories, and that each sub-group could come together in a forum such as this and present their findings, long- and short-term plans, and needs. Under that procedure, we could get a fairly good fix on what is going on. I think this is a great start but I think we have a long way to go before we know what is going on in the Federal Government in terms of Federal human nutrition research. For example, Victor Herbert mentioned this morning that the VA was presenting only 5 papers selected out of 50 potential groups. This gives you an idea of the kinds of the range of things we have not heard about. USDA spent a few minutes talking about highlights of what is going on in each of our centers. We did not cover the huge programs of HHS; we talked only about parts of the program in cardiovascular diseases, cancer, food science, nutritional status monitoring, and so on. We really do not have a fix in these areas yet, we have just made a start. A good start I might say, but we have long way to go.

Dr. Victor Herbert: Something came up about priorities and Walter Mertz touched on it. I would like to extend that just a little bit. I also believe in priorities, but my one fear is that whenever one fixes priorities, Congress or the President will say there are X dollars to be divided up and you nutrition scientists fight over how much HHS will get, how much USDA will get, and how much this one and that one will get. That serves a bad purpose. Each of the Federal agencies has to realize that if any Federal agencies' dollars for nutrition are cut, we all bleed. Every agency bleeds because there is a diminution in resulting nutrition information from which we all profit; when any agencies' nutrition budget is cut, all of the agencies suffer.

Dr. Artemis Simopoulos: Dr. Anderson.

Dr. James Anderson: I feel really awkward getting up because I do not know anything about planning but I will make a couple of comments. The National Diabetes Advisory Board has had 3 or 4 intensive workshop conferences where they have tried to identify areas of need, gaps in knowledge, and tried to look at how research could be directed in those areas. I think that sort of intensive working conference, where people present ideas, those ideas are summarized, and recommendations grow out of that, would be a very useful thing in the nutrition area. It seems to me, and again, this is a very naive statement, that it is so controversial to try to develop nutrition goals (whatever they may be called) for the country, that we ought to focus on research needs. Maybe at some point in time there will be a consensus about nutrition goals for the country; but we can certainly reach a consensus on areas of nutrition research needs that are crying for attention.

Dr. Artemis Simopoulos: Thank you, Jim. Dr. Sandstead.

Dr. Harold Sandstead: It seems to me that our task is actually two fold. I think one of the most beneficial aspects of this meeting was the exchange of scientific information among ourselves. I found out what other people were doing, and they found out a little bit about what I was doing. I think we need to continue that activity, independently perhaps, of the planning process. I view the planning process as a exercise that is often not particularly scientific; it is more of a sociologic experience, which will hopefully result in something that can point the way for the future. Planning should go on for a long time, and it should go on continually with multiple meetings over a period of time. It should lead to an evolutionary plan that will provide guidance not only to the Congress, but also to the Executive, and the heads of the various agencies. The way human nutrition presently works in the Federal Government and throughout the country, makes it a sort of a big happening--each agency is doing its own thing without too much regard to what others are doing. In view of the situation, it is fortunate that we work together, as individual scientists. Because of mutual interests, we develop collaboration and thus work together.

It seems to me that the decisions that guide agencies with regard to human nutrition too often are based on non-nutritional considerations. Nutrition may either benefit or suffer depending on their independent factors. This being the case, I believe it is important that planning be a continual process that allows for contingencies. At the same time, we should continue to meet on a regular and, at least, an annual basis, for scientific information exchange. With the exchange of scientific information, planning, at least between individual scientists, will probably happen while the long process of national planning goes on.

Dr. Artemis Simopoulos: Thank you. Dr. Rosenberg.

Dr. Irwin Rosenberg: I would just try to address some of the "planaphobia" which has been suggested here by Alfred Harper and perhaps by Walter Mertz. I think we all share the concern that planning, if carried too far, can become so mission oriented that the basic science underpinnings that we all value and recognize would be limited and perhaps squashed. However, if that happened it would just be a bad plan. In other words, I could see a plan of research evolving which recognized that an organization like DOD is more constrained in its mission in regard to nutrition research than an organization such as NIH; one could recognize that there are places within the larger plan where clear mission-oriented planning was appropriate, and there were other places where basic science oriented planning was appropriate. It would have to be recognized that the appropriate mix of those kinds of things is essential if a plan is to evolve.

A good plan could preserve the integrity of basic science research and scientist generated research if the plan clearly recognizes that all developments are going to be dependent on such research.

I will also make a comment about the utility of a yearly meeting of this kind for information exchange. I wonder if a yearly meeting really is necessary for this kind of information exchange. Perhaps regular meetings are useful. I would raise some questions about whether we need to meet every year and I would also question how such a meeting will be paid for. Finally, in response to Dr. Carter's comments, I think that if we are to have other workshops that focus on aspects of the plan, there is another kind of workshop to which we ought to give some consideration in addition to workshops that the Subcommittee may wish to have that bring in a broad spectrum of consumer and public information. These are workshops discussing some common themes that have developed here over the last couple of days; interests that we keep bringing up. One example, that happens to be parochial, comes to mind, and that is a workshop relating to the concept and methods of bioavailability studies. We have heard over and over that one of the useful outcomes of this conference would be a meeting of representatives of this body and a few others who are concerned with those methods; to decide when it is appropriate to use in vitro techniques, when it is appropriate to use animal techniques, and when we must use human bioavailability methods and which to use.

Dr. Mary Carter: Before I comment, let us hear from this gentleman.

Dr. John Vanderveen: I think there is one aspect that we have not discussed today; in looking at what Congress is thinking, perhaps we ought to pay some attention to research priorities. Congress and the administration are obviously concerned about resources and they are becoming much more involved these days with actual scientific issues, despite Congressman Brown's suggestions yesterday that he is going to leave this to the scientists. FDA, as an action agency, and other action agencies within the Federal Government face this more and more each day. We are talking at this conference about planning the expenditures of resources that is approved by Congress and funded by the public. I would not want to suggest that all programs have to be oriented in someway to support the activities that the Congress

perceives, the Administration forsees, or the action agencies envision; nevertheless there is an increasing involvement of the Congress and a part of the public in these issues. One of the things that, to a large degree, is missing from this meeting is a discussion of the question of what the needs of the action agencies are in trying to carry out the activities that are being forced upon them, not only by every day business but also by the Congress and the Administrations as they come and go. I suggest that future conferences could include more discussions of what the needs are of these mandated programs.

At lunch today we talked about end-stage renal disease and what nutrition-related decision needs to be made relative to this disease. Research is ongoing, but perhaps a discussion in groups like this can identify data that exist in various locations, but have not been brought together. Obviously, one of the questions is: do you set up a new program or do you try to get those answers from existing research programs. Can you encourage scientists, just by discussion, to modify or focus their research to try to provide answers. We, as an action agency, could probably come up with a list of 50 such topics. For example, we still have not obtained answers as to whether we ought to more carefully regulate diets promoted for very rapid weight loss (very low calorie diets). I believe Congress is becoming more and more concerned about such technical issues. That was obvious from the hearings on fortification; it is obvious from other hearings that are being planned. So, I would suggest that this area not be overlooked.

Dr. Elaine Feldman: I have been listening and have a couple of thoughts to express. We are talking in part about implementation of a plan or strategies, and we are talking about nutrition most of the time. We consume "nutrition" not as chemicals but as food. It seems to me that somewhere along the line we are going to have to consider the food industry and include them in an appropriate way in what we are doing. This includes not just the food companies, but also supermarkets or restaurants where one purchases the food, the fast food outlets, and so on. That is a segment of the problem that I have not heard brought up, although we have talked about scientific professionals who are not in the Federal Government, and we have talked about the consumer and the lay public. It seems to me there is a gap in terms of who makes the food and who offers the food to the public, and this segment is going to have to be considered in some way.

Turning to another track, brought to mind by the talk about diabetes and end-stage renal disease, a problem we physicians encounter all of the time in talking about nutrition to the public or large groups is that we do not have a disease, we do not have a focus. Years ago, the words "deficiency diseases" had meaning. In other parts of the world there is significant malnutrition, but in the U.S. we have a much more diffuse and broad problem. Consequently, we do not have working with or for us a diabetes lobby or support group; we cannot agree among ourselves whether the Heart Association or some other group would be representative of what we want to say. I do not think we can change that at all, but I think that is part of what makes planning in nutrition more difficult.

APPENDIX I

Charter

Joint Subcommittee on Human Nutrition Research

JOINT SUBCOMMITTEE ON HUMAN NUTRITION RESEARCH (JSHNR)
of
Committee on Health & Medicine (CHM)
and Committee on Food & Renewable Resources (CFRR)

Federal Coordinating Council for Science
Engineering & Technology (FCCSET)

CHARTER

Because of the vital importance of the benefits from human nutrition research to the welfare of the American people and the world population, it is essential that the nutrition research efforts of the Federal agencies be mutually reinforcing.

In recognition of this need, the Committee on Health and Medicine (CHM) and the Committee on Food and Renewable Resources (CFRR) hereby establish a Joint Subcommittee on Human Nutrition Research (JSHNR).

Scope: The Subcommittee is concerned with: (1) all federally supported or conducted research on nutrition with emphasis on human nutrition; and (2) professional personnel needs in nutrition research and education. This includes:

- Basic physiological and biochemical mechanisms for the digestion, absorption, metabolism, and transport of nutrients; the role of food ingredients in human health and performance and in the prevention and treatment of disease.

- Nutrient composition of foods; the effects of storage, processing, and packaging; and the biological availability of nutrients in the foods at the time of consumption.

- Determinants of dietary practices and methods for educating the public about dietary practices.

- Food consumption patterns and nutritional status of the general population and of special high-risk subgroups within the population; evaluation of the nutritional impacts of various intervention strategies and public policies.

- The professional personnel to carry out research on human nutrition; training programs in nutrition research and nutrition education in medical schools, dental schools, schools for allied health professionals, schools of nutrition, teachers' colleges, and schools of food and agriculture; nutrition education at the primary and secondary school level; and the manpower needs for education of the public.

Purpose and Function: The purpose of JSHNR is to increase the overall effectiveness and productivity of research efforts in nutrition. In fulfilling this purpose, the Subcommitte will:

a. Improve planning, coordination, and communication among Federal agencies engaged in research on nutrition.

b. Develop and update plans for Federal research programs to meet current and future domestic and international needs for nutrition.

c. Collect, compile, and disseminate information on nutrition research.

d. Prepare reports describing activities, findings, and recommendations of the Subcommittee.

Organization of the Committee

The Co-Chairpersons of JSHNR will serve a term of two years and be selected by mutual agreement between the Chairpersons of CHM and CFFR. The Executive Secretary will be designated by the Co-Chairpersons of the Subcommittee (JSHNR). Chairpersons of task forces or working groups of the Subcommittee will arrange for staff assistance from their own agencies.

In addition to the Co-Chairpersons, the Subcommittee will include representation from:

- Agency for International Development
- Department of Agriculture
- Department of Commerce (NOAA)
- Department of Defense
- Department of Health, Education, and Welfare
- Federal Trade Commission
- National Science Foundation
- Veterans Administration
- Office of Science and Technology Policy -- ex officio

Other Federal agencies may participate, as appropriate, upon invitation by the JSHNR Co-Chairpersons.

The Subcommittee will follow a schedule of periodic meetings and hold special meetings at the call of the Co-Chairpersons. Agendas for meetings will be made available for members prior to each meeting. Minutes of meetings will be prepared by the Executive Secretary and distributed to all members of the Subcommittee, to leaders of its task forces or working groups, and to the Executive Secretary of FCCSET, CHM, and CFRR.

The Subcommittee will have such task forces or working groups as established by the Co-Chairpersons for the conduct of required Subcommittee work.

Compensation

All members will be full-time Federal employees who are allowed reimbursement for travel expenses by their agencies plus per diem for subsistence while serving away from their duty stations in accordance with Standard Government Travel Regulations.

Annual Cost Estimates

Estimated annual cost of operating the Subcommittee, excluding staff support, is $1,000. Estimated annual cost of staff support is one person-year at $20,000.

Reports

The Subcommittee shall prepare a report for the Chairperson of FCCSET, CHM, and CFRR not later than sixty days after the end of each fiscal year. This report shall contain as a minimum the Subcommittee's functions, a list of members and their business addresses, the dates and places of meetings, and a summary of the Subcommittee's activities and recommendations during the year.

Determination

I hereby determine that the formation of the Subcommittee on Human Nutrition Research is in the public interest in connection with the performance of duties imposed on the Executive Branch by law, and that such duties can best be performed through the advice and counsel of such a group.

Approved:

Donald S. Fredrickson, M.D.
Chairman
Committee on Health and Medicine

for DAVID G. UNGER
M. Rupert Cutler
Chairman
Committee on Food and Renewable Resources

SEP 28 1978
DATE

Frank Press
Chairman
Federal Coordinating Council for
Science, Engineering, & Technology

APPENDIX II

Obesity As An Independent Risk Factor for Cardiovascular Disease: A 26-year Follow-up of Participants in the Framingham Heart Study

By

Helen B. Hubert, M.P.H., Ph.D., et al.

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Obesity as an Independent Risk Factor for Cardiovascular Disease: A 26-year Follow-up of Participants in the Framingham Heart Study

HELEN B. HUBERT, M.P.H., PH.D., MANNING FEINLEIB, M.D., DR.P.H., PATRICIA M. MCNAMARA, AND WILLIAM P. CASTELLI, M.D.

SUMMARY **The relationship between the degree of obesity and the incidence of cardiovascular disease (CVD) was reexamined in the 5209 men and women of the original Framingham cohort. Recent observations of disease occurrence over 26 years indicate that obesity, measured by Metropolitan Relative Weight, was a significant independent predictor of CVD, particularly among women. Multiple logistic regression analyses showed that Metropolitan Relative Weight, or percentage of desirable weight, on initial examination predicted 26-year incidence of coronary disease (both angina and coronary disease other than angina), coronary death and congestive heart failure in men independent of age, cholesterol, systolic blood pressure, cigarettes, left ventricular hypertrophy and glucose intolerance. Relative weight in women was also positively and independently associated with coronary disease, stroke, congestive failure, and coronary and CVD death. These data further show that weight gain after the young adult years conveyed an increased risk of CVD in both sexes that could not be attributed either to the initial weight or the levels of the risk factors that may have resulted from weight gain. Intervention in obesity, in addition to the well established risk factors, appears to be an advisable goal in the primary prevention of CVD.**

THE IMPORTANCE of body weight, body mass and other measures of adiposity in the prediction of cardiovascular disease (CVD) has been the subject of long-standing debate. Many studies have shown that the incidence of certain types of CVD, particularly coronary heart disease and stroke, is greater in heavier persons,[1-6] but only a few suggest that any obesity index makes an additional contribution to risk once the levels of coexisting risk factors are taken into account.[1, 2, 4] Obesity is associated with elevated blood pressure, blood lipids and blood glucose,[7-11] and changes in body weight are coincident with changes in these risk factors for disease.[12, 13] Thus, the consensus has been that the increased risk among heavier persons is due primarily to the influence of the associated risk factor profile and not to the degree of obesity per se. The existing data have also been interpreted to suggest that obesity is benign when it exists without other major risk factors for CVD.

In this report, we reexamine the obesity question and describe the influence of relative weight on the 26-year incidence of CVD in Framingham men and women. Earlier results from this study suggested that the degree of obesity is not a potent independent risk factor for CVD in general, particularly among women.[14, 15] However, these conclusions were based on analyses of the influence of relative weight over shorter periods of follow-up and may not have conveyed the true impact of disease risk.

Such a reevaluation appears timely in view of the current revisions to the original Metropolitan Life Insurance Company desirable weight tables.[16] These desirable weights, derived from the mortality experiences of subscribers, have been revised upward because new data on insured lives[17] suggest that it is healthier to be heavier than once thought. Recent analyses of long-term mortality in Framingham indicate, however, that this may not be so; minimal mortality occurs at previously published levels of desirable weight.[18] Although recent statistics indicate that the general U.S. population, particularly men, has been getting heavier over the last few decades,[19, 20] considerably more data are needed to evaluate the implications of this trend. Likewise, revisions to the desirable weight tables seem premature, because the complex relationships between body weight and health or disease are so poorly understood. This reappraisal of the impact of relative weight on cardiovascular morbidity in Framingham further emphasizes the need for caution, because health-related issues other than total mortality should be considered in arriving at acceptable levels of desirable weight.

Methods

The Framingham Heart Study population has been examined and followed biennially for the development of CVD since 1948.[21] In this report we present the morbidity experience of 2252 men and 2818 women, ages 28–62 years, who were free of clinically recognizable CVD at the first study examination, which took place between 1949 and 1950. Manifestations of CVD included coronary heart disease, congestive heart failure, stroke and intermittent claudication.

For the purposes of this report, the subjects were classified by weight and other risk attributes at the initial examination only and observed over 26 years for the development of CVD. The obesity index chosen to characterize the population was Metropolitan Relative Weight (MRW), or percentage of desirable weight (the ratio of actual weight to desirable weight × 100). Desirable weight for each sex was derived from the

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1959 Metropolitan Life Insurance Company tables[16] by taking the midpoint of the weight range for the medium build at a specified height. Since desirable weights were reported for subjects wearing both clothes and shoes, these figures were adjusted in order to apply them to Framingham subjects, who were weighed and measured in a dressing gown and without shoes (table 1).

Other characteristics of interest at the initial examination were systolic blood pressure, measured in the left arm of the seated subjects with a mercury sphygmomanometer and a 14-cm cuff long enough to fit the most obese arm; serum cholesterol concentration, determined by the method of Sperry;[22] the number of cigarettes smoked per day, assessed by a physician-administered medical history questionnaire; glucose intolerance, defined by a casual blood glucose level of at least 120 mg%, the presence of glycosuria or a definite history of diabetes; and left ventricular hypertrophy on a 13-lead ECG.

Criteria for each cardiovascular outcome during follow-up were standardized,[23] and decisions regarding diagnosis were made by a panel of Framingham investigators. Coronary heart disease included diagnoses of (1) angina pectoris, evidenced by a typical history of chest pain on a physician-administered questionnaire; (2) myocardial infarction, determined by specified electrocardiographic changes, diagnostic elevation of serum enzymes with prolonged ischemic chest pain, or autopsy; (3) coronary insufficiency, defined as prolonged ischemic chest pain accompanied by transient ischemic abnormalities on the ECG; and (4) sudden (in less than 1 hour) or nonsudden coronary death. Congestive heart failure was indicated when at least two major or one major and two minor diagnostic conditions existed concurrently upon examination.[23] The major stroke end point of interest was atherothrombotic brain infarction, defined as the sudden onset of a localizing neurologic deficit lasting over 24 hours without evidence of embolism or hemorrhage. Intermittent claudication was diagnosed from subjective responses to questions on calf cramping during exertion.

TABLE 1. *Adjusted Desirable Weights for the Framingham Heart Study Participants*

Height (inches)	Weight (lb)	
	Men	Women
55		94
56		97
57		100
58		103
59		106
60	116	109
61	119	112
62	122	116
63	125	120
64	128	124
65	131	128
66	135	132
67	140	136
68	144	140
69	148	
70	152	
71	157	
72	161	
73	166	
74	170	

Preliminary analyses of the data consisted of calculating crude incidence rates of disease by level of MRW. More formal statistical methods used to assess the influence of MRW independently of the coexisting levels of the major cardiovascular risk factors relied upon multivariate logistic regression procedures[24] in which the probability of an event was described as a function of several attributes measured at entry to the Framingham Study. Regression coefficients generated by the logistic model measured the strength of the association between adiposity and the probability of disease after adjustment for age and the other risk factors. The coefficients divided by their standard errors provided tests of significance to indicate whether these relationships were significantly different from zero ($p \leq 0.05$ when $z \geq 1.96$). Standardized coefficients that adjust for differences in measurement units between variables were also calculated to show the impact of weight relative to the other risk factors for disease.

Results

During the 26-year follow-up, 870 men and 688 women developed clinically recognizable CVD. Although some subjects had more than one manifestation of disease, coronary heart disease accounted for a large proportion of the events, 75% and 66% in men and women, respectively. Congestive failure occurred in 183 men and 165 women and atherothrombotic stroke in 106 men and 103 women. Intermittent claudication was diagnosed more often in males than in females (171 vs 112).

At entry to the study, the disease-free Framingham cohort appeared to be considerably overweight. On the average, men were 18.9% and women 20.5% above desirable weight. Although the distributions of initial relative weights were very similar in men younger than 40 years, 40–49 years and 50 years or older, women appeared to be heavier in each subsequent age group (fig. 1). Clearly, a larger proportion of females than males were at the upper end of the weight distribution, particularly among the 50–62-year-olds.

Figure 2 shows sex- and age-specific crude incidence rates for total CVD over 26 years by MRW at entry to the study. For this purpose only, relative weight was categorized as less than 110, 110–129, and 130 or over; the middle category spanned evenly over the mean weights for men and women. The risk of CVD increased in both men and women with increasing MRW. However, the association of weight to inci-

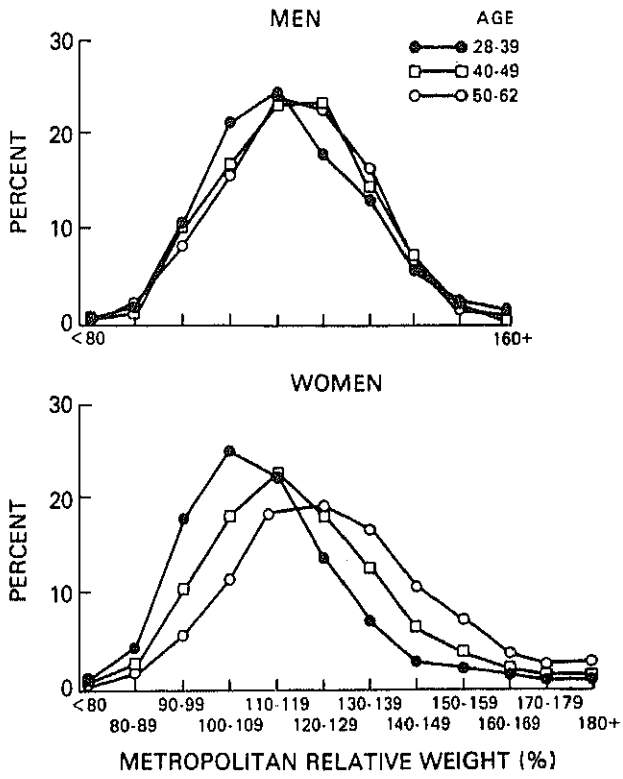

FIGURE 1. *Age- and sex-specific distributions of Metropolitan Relative Weight at the initial Framingham examination.*

dence was most pronounced in those younger than 50 years. This observation was borne out in logistic regression analyses by sex and age group, where the impact of weight was similar in those younger than 40 years and 40–49 years, but greater in these two age groups combined than in the older segment of the cohort.

Similar relationships were evident between MRW and coronary disease, the most frequent manifestation of CVD (fig. 3). Incidence also increased with increasing MRW, and the gradient of risk was steeper in the younger men and women. Among men younger than 50 years, the heaviest group experienced twice the risk of coronary disease compared with the leanest group. The risk was increased 2.4-fold among obese women of similar age. The relationships for risk of myocardial infarction were similar to those for total coronary disease (fig. 4). However, there was a much stronger gradient of risk for sudden death with increasing MRW in each age group in both sexes (fig. 5). In fact, these crude rates suggest that the impact of weight on risk may be most pronounced for this outcome. Figure 6 shows that the 26-year incidence of congestive heart failure in the younger men and women increased 2.5- to 3-fold from the leanest to the heaviest subjects. Unlike coronary disease, it appeared that the risk of congestive failure in women was elevated only in the most obese group. MRW had a greater impact on the incidence of atherothrombotic stroke in women than in men (fig. 7). Women younger than 70 years who were 30% or more over desirable weight experienced over four times the stroke rate of the leanest group.

However, not every cardiovascular end point was consistently related to MRW. The 26-year incidence of intermittent claudication, indicative of peripheral vascular disease, did not appear to be clearly related to the degree of overweight in either men or women (fig. 8).

Multivariate logistic regression analyses were undertaken to ascertain whether the strong relationships between weight and disease would persist upon adjustment for the influence of the coexisting levels of the major CVD risk factors. These included age, systolic blood pressure, serum cholesterol, cigarettes per day,

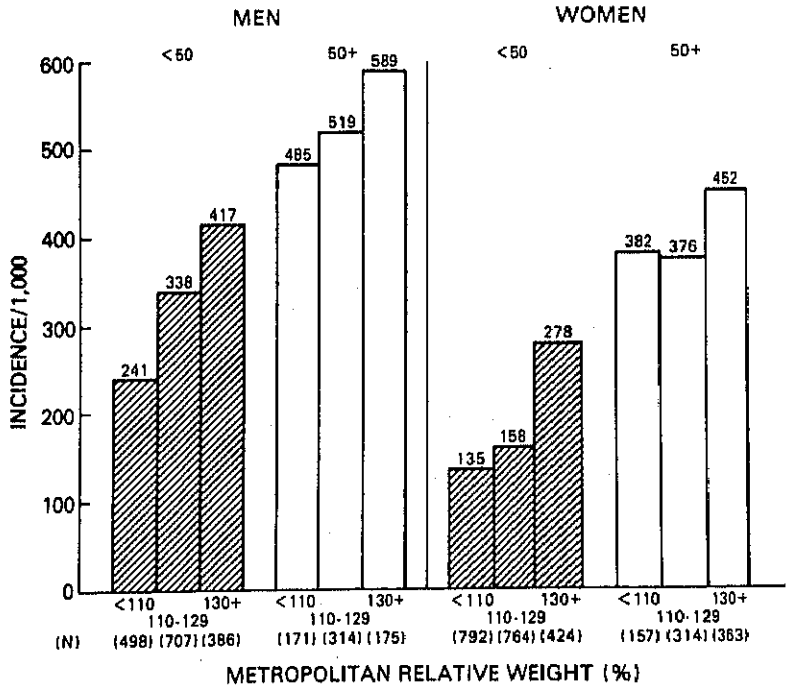

FIGURE 2. *Twenty-six-year incidence of cardiovascular disease by Metropolitan Relative Weight at entry among Framingham men and women younger than age 50 years and age 50 years or older. N = the number at risk for an event. Numbers above the bars give the actual incidence rates per 1000.*

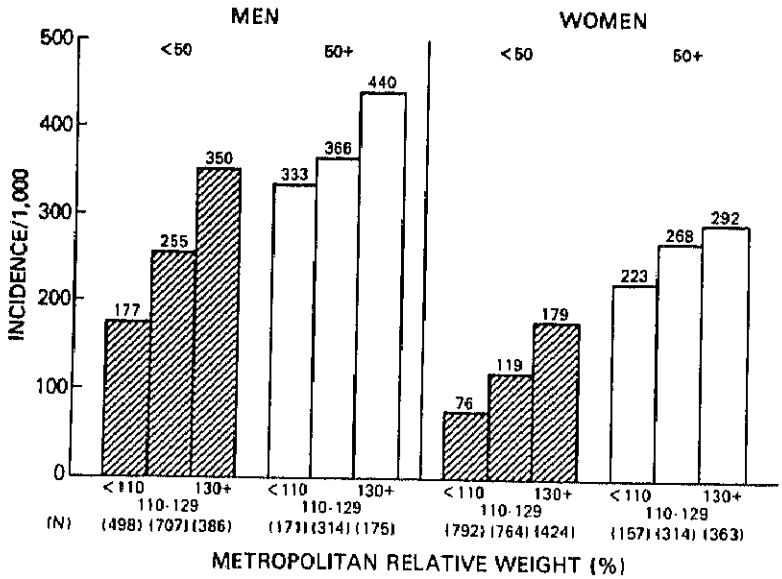

FIGURE 3. *Twenty-six-year incidence of coronary heart disease by Metropolitan Relative Weight at entry among Framingham men and women younger than age 50 years and age 50 years or older. N = the number at risk for an event. Numbers above the bars give the actual incidence rates per 1000.*

glucose intolerance (no, yes), and electrocardiographic left ventricular hypertrophy (no, possible, definite). In all regression procedures, MRW and age were entered as continuous rather than categorical variables. The results in table 2 indicate that MRW was a significant predictor of total CVD in both men and women after adjustment for risk factors. Although independent relationships were apparent for angina, coronary disease other than angina, congestive failure, and coronary death in both sexes, the probabilities of myocardial infarction, atherothrombotic stroke, and cardiovascular death were associated with the degree of obesity in women only. (The regressions that adjusted for age alone yielded statistically significant associations between all end points and obesity in both sexes.) MRW was clearly a strong predictor of sudden death in males. The fact that MRW was not significantly associated with sudden death in females could be attributed to the small number of events in this group. The coefficients in table 2 suggest that the strength of the association was greatest for sudden death in men and congestive failure in women and that the relationship between MRW and coronary disease was stronger in males than in females because of the greater influence of this characteristic on the development of angina in men. Inclusion of additional risk factors (cardiac enlargement, heart rate and vital capacity) in the regression for congestive failure did not alter the relationship between weight and disease. Although it has been suggested that lean compared to obese hypertensives may be at increased risk of death over 8 years of follow-up in Framingham (unpublished data), further analyses of 26-year incidence of CVD and coronary death presented no evidence to indicate

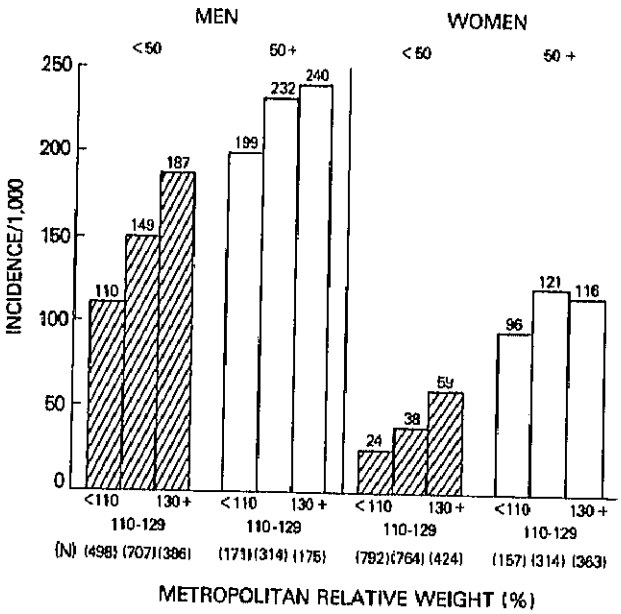

FIGURE 4. *Twenty-six-year incidence of myocardial infarction by Metropolitan Relative Weight at entry among Framingham men and women younger than age 50 years and age 50 years or older. N = the number at risk for an event. Numbers above the bars give the actual incidence rates per 1000.*

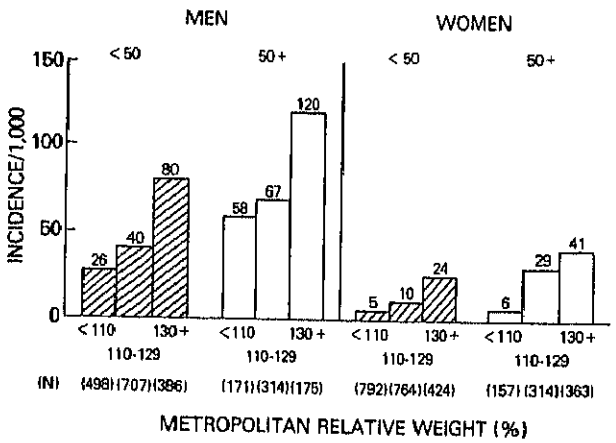

FIGURE 5. *Twenty-six-year incidence of sudden death by Metropolitan Relative Weight at entry among Framingham men and women younger than age 50 years and age 50 years or older. N = the number at risk for an event. Numbers above the bars give the actual incidence rates per 1000.*

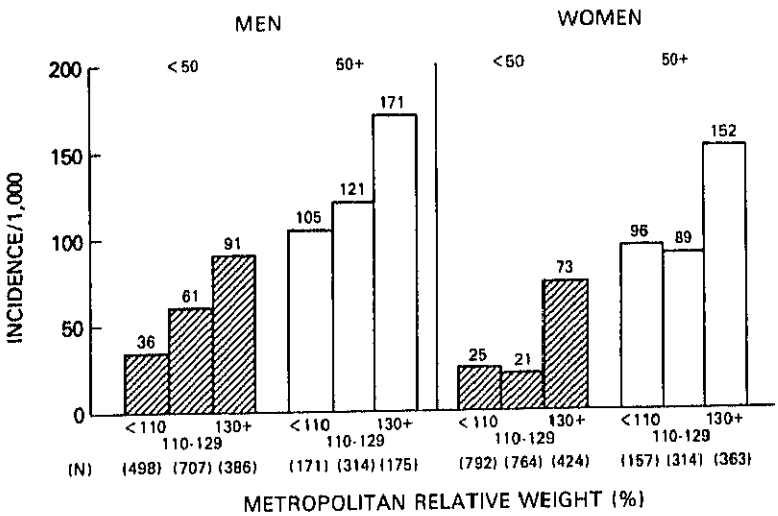

FIGURE 6. *Twenty-six-year incidence of congestive heart failure by Metropolitan Relative Weight at entry among Framingham men and women younger than age 50 years and age 50 years or older. N = the number at risk for an event. Numbers above the bars give the actual incidence rates per 1000.*

that there was such an interaction effect between weight and its strongest correlate, blood pressure.

The magnitude of the standardized regression coefficients indicated that degree of obesity was one of the best predictors of total CVD in women (table 3). In this group, weight ranked only behind age and blood pressure, while in men it ranked behind all the other risk factors. MRW among males was a better predictor of manifestations of coronary heart disease than blood pressure, cigarette smoking, glucose intolerance or electrocardiographic left ventricular hypertrophy.

It has been argued that obesity does not convey an increased risk of disease unless it is accompanied by elevations in such characteristics as blood pressure or blood lipids. This hypothesis was examined by calculating CVD incidence rates by level of MRW in men and women younger than 50 years of age who were free of risk factors at entry into the study (fig. 9). That is, they were normotensive, had serum cholesterol levels less than 250 mg/dl, did not smoke cigarettes, and had no evidence of glucose intolerance or left ventricular hypertrophy on the ECG. It is not surprising that only 8% of the men and 18% of the women in the highest weight class were free of risk factors. In the subpopulation without major risk factors for disease, CVD incidence rose with increasing weight in both men and women, although the gradient of risk was clearly steeper in males than females. Moreover, logistic regression analysis in this group showed that the strength of the association between MRW and disease in both sexes was at least as great as that for men and women in the total cohort. The MRW coefficients for these males and females were 0.016 and 0.010, respectively, compared with a coefficient of 0.009 for the total population shown in table 2. Thus, the effects of obesity could be demonstrated even in those without major risk factors for disease.

The relationship of weight change to CVD incidence was examined by comparing self-reported weight at age 25 with weights at the initial Framingham examination. Although recall may be subject to some degree of bias, there is evidence from the NHLBI Twin Study[25] and the Honolulu Heart Program (personal communication) that weights reported many years after age 25 years correlate fairly well with actual weights or weights reported close to that age. In this study, weight change was defined as the difference between MRW at exam 1 and MRW at age 25 years. Logistic regression analyses showed that change in MRW was positively and significantly related to risk of CVD over 26 years in both sexes even after adjustment for the effects of MRW at age 25, age at exam 1, and risk factor levels. The relative odds of developing disease corresponding to degrees of change in relative weight were calculated from the multivariate regression equation. Although women, on the average,

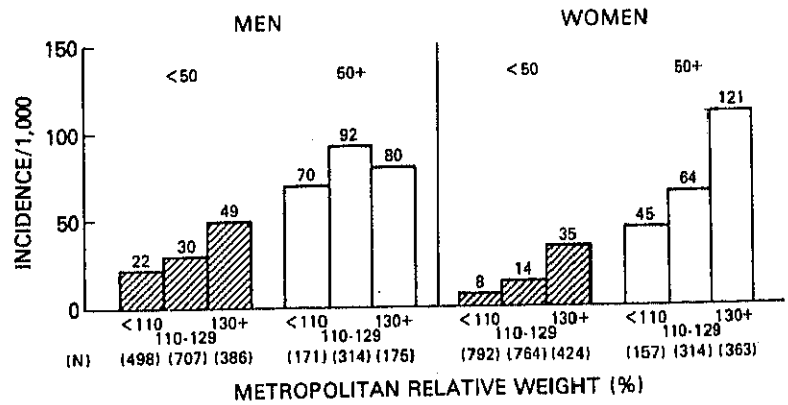

FIGURE 7. *Twenty-six-year incidence of atherothrombotic brain infarction by Metropolitan Relative Weight at entry among Framingham men and women younger than age 50 years and age 50 years or older. N = the number at risk for an event. Numbers above the bars give the actual incidence rates per 1000.*

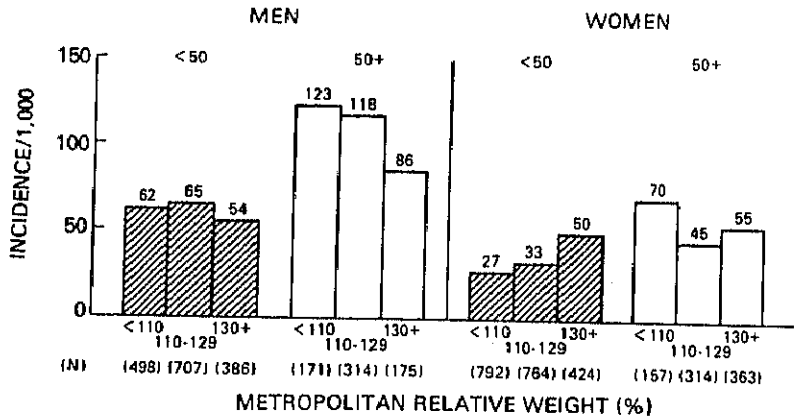

FIGURE 8. *Twenty-six-year incidence of intermittent claudication by Metropolitan Relative Weight at entry among Framingham men and women younger than age 50 years and age 50 years or older. N = the number at risk for an event. Numbers above the bars give the actual incidence rates per 1000.*

gained more weight than men between age 25 and entry, figure 10 shows that the net effect of weight change was greater in males than females. Nonetheless, one could conclude from these data that weight gain into the middle and older ages conveyed an increased risk of disease and weight loss a decreased risk of disease that could not be attributed either to MRW at age 25 years or the levels of the risk factors that may have resulted from weight change.

Discussion

These data clearly show that the degree of obesity in Framingham men and women was an important long-term predictor of CVD incidence, particularly among the younger members of the cohort. Moreover, obesity in both sexes did not exert its influence on the risk of coronary disease or congestive failure solely through its association with the coexisting risk factors. In women, significant independent relationships were evident for atherothrombotic stroke as well. The lack of association between weight and incidence of intermittent claudication, on the other hand, suggests that the cause of this disorder may be somewhat different from that of the other cardiovascular diseases. These results might also be attributed to underdiagnosis of intermittent claudication in heavier subjects who may not walk or exercise to elicit symptoms with the same frequency as leaner subjects.

It also appears that obesity predisposed to premature CVD in Framingham. Plots of the actuarial life tables for the younger members of the cohort (those younger than 50 years of age at entry to the study) show higher risks for the heaviest compared with the leanest group throughout the 26-year follow-up period (fig. 11). However, differences were more pronounced in the younger men than women.

Weight was a relatively potent risk factor for total CVD in women. Only age and blood pressure were more powerful predictors in this group. Male–female differences regarding the impact of obesity on disease

TABLE 2. *The Association Between Metropolitan Relative Weight at Entry and Cardiovascular Disease Incidence Over 26 Years in Framingham Men and Women*

Event	Multivariate logistic regression coefficients for MRW	
	Men (n = 2197)	Women (n = 2714)
CHD	0.012‡ (636)	0.008† (437)
AP	0.014‡ (336)	0.007* (276)
CHD other than AP	0.009† (514)	0.010‡ (261)
MI	0.006 (372)	0.010† (161)
Death from CHD	0.009* (266)	0.010† (132)
Sudden death from CHD	0.016† (120)	0.010 (45)
Congestive heart failure	0.014† (177)	0.015‡ (161)
Atherothrombotic stroke	0.004 (105)	0.012† (100)
Death from CVD	0.006 (395)	0.008† (263)
Total CVD	0.009† (849)	0.009‡ (667)

Regressions include adjustments for age, systolic blood pressure, serum cholesterol, cigarettes/day, glucose intolerance, and electrocardiographic left ventricular hypertrophy at exam 1.
The number of events is given in parentheses.
*Coefficient is significantly different from zero, $p < 0.05$.
†Coefficient is significantly different from zero, $p < 0.01$.
‡Coefficient is significantly different from zero, $p < 0.001$.
Abbreviations: MRW = Metropolitan Relative Weight; CHD = coronary heart disease; AP = angina pectoris; MI = myocardial infarction; CVD = cardiovascular disease; n = number at risk.

TABLE 3. *The Association Between the Major Risk Factors and Disease Incidence Over 26 Years in Framingham Men and Women*

Risk factors	Standardized logistic regression coefficients			
	Men (n = 2197)		Women (n = 2714)	
	CHD	CVD	CHD	CVD
Age	0.325	0.469	0.339	0.390
Systolic blood pressure	0.176	0.311	0.281	0.332
MRW	0.200	0.143	0.175	0.199
Serum cholesterol	0.345	0.309	0.266	0.197
Cigarettes/day	0.170	0.232	0.035*	0.139
Glucose intolerance	0.111	0.220	0.109	0.100
ECG-LVH	0.098	0.215	0.016*	0.084*

*Coefficients not significantly different from zero, $p > 0.05$.
Abbreviations: CHD = coronary heart disease; CVD = cardiovascular disease; MRW = Metropolitan Relative Weight; ECG-LVH = electrocardiographic left ventricular hypertrophy; n = number at risk.

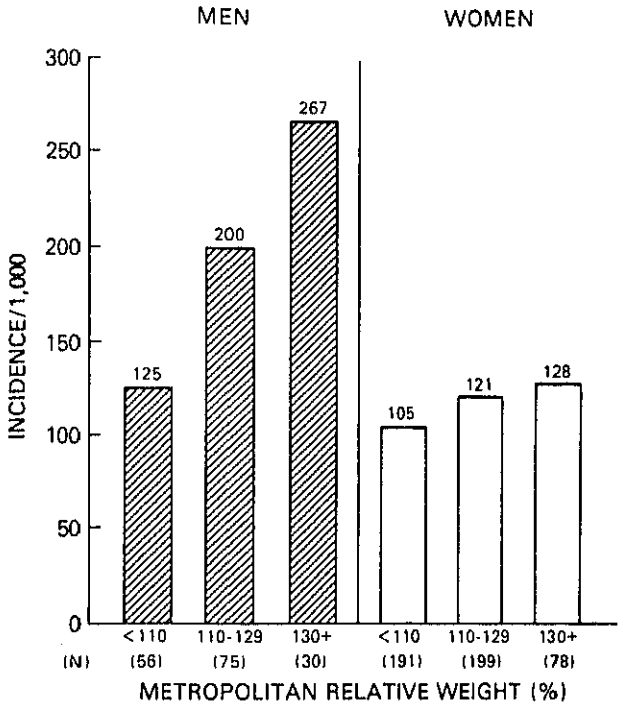

FIGURE 9. *Twenty-six-year incidence of cardiovascular disease by Metropolitan Relative Weight at entry among Framingham men and women younger than 50 years of age who were normotensive, had cholesterol levels less than 250 mg/dl, did not smoke cigarettes, and had no evidence of glucose intolerance or electrocardiographic left ventricular hypertrophy. N = the number at risk for an event. Numbers above the bars give the actual incidence rates per 1000.*

might be explained by differences in the operation of the risk factors or in the causal pathways leading to disease. These hypotheses have been suggested by other data,[26, 27] but additional factors may be responsible for the differences observed here. It is possible that the disparity in the weight distributions (that is, proportionately more women than men were extremely overweight) influenced the results to a certain degree. Relative weight also may have represented a somewhat different measure of body mass in each sex, since excess weight resulted from muscularity more often in males than females. This point may be illustrated by additional analyses that describe the influence of other measures of obesity on risk. These show that while MRW was not an independent predictor of myocardial infarction in Framingham men, subscapular skinfold measurements were significantly and independently associated with this outcome. Thus, it may be misleading to suggest that obesity in men did not play an important role as a precursor to infarction.

Age differences in the contribution of obesity to risk have also been noted by others.[1-4] Similarly, other risk factors for disease do not predict as well at older ages as at younger ages.[4-28] Selection has been suggested as an explanation for such findings. Here, the older, heavier subjects may have been a selective group, because they remained resistant to the influence of obesity during earlier years. However, weights at older ages may be less typical of the lifetime exposure to obesity, which may be important in determining risk. If, as suspected, age at onset and duration of obesity play a part in explaining the observed associations with disease, then earlier measurements may more accurately classify individuals into risk categories than those made in later years. The fact that certain risk factors correlated more strongly with relative weight at younger than older ages also supports the latter theory.

Population studies have shown that the extremely lean as well as the most obese are at increased risk of dying over a specified time.[29] Such observations suggest that the relationships found in this study might be overstated and attributable to the phenomenon of competing risks. That is, the leaner subjects may have appeared to be at lower risk due to the fact that they died from other causes before they could develop CVD. A few simple approaches to evaluating the plausibility of such an explanation indicated that competing risks could not account for the weight-disease relationships found in Framingham men and women. The first approach entailed estimating the proportion of subjects who died of other causes but who would have been expected to develop CVD if they had lived long enough.[30] The calculation of new incidence rates by level of MRW showed risks associated with increased MRW that were diminished, but only negligibly. Assuming that the leanest subjects might already be ill and die of causes other than CVD, reanalysis of the data also was undertaken including only subjects with MRW of 100 or more. The results showed associations with CVD that were at least as strong as those originally obtained.

Not only was there a powerful relationship of MRW to disease risk in Framingham, but also, the change in

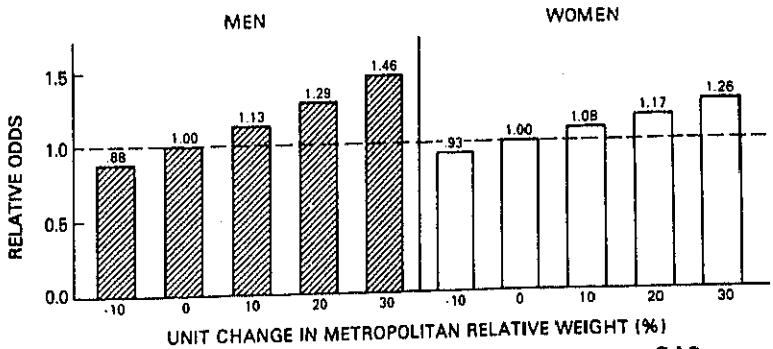

FIGURE 10. *The relative odds of developing cardiovascular disease corresponding to degrees of change in Metropolitan Relative Weight between age 25 years and entry into the Framingham Study. The odds ratios reflect adjustments for the effects of relative weight at age 25 years and age and risk factor levels at exam 1.*

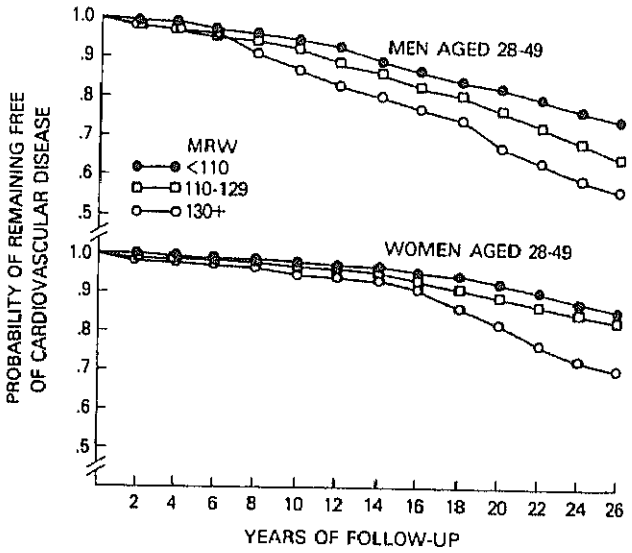

FIGURE 11. *The probability of remaining free of cardiovascular disease at each follow-up examination by Metropolitan Relative Weight (MRW) at entry.*

MRW after the young adult years made an independent contribution to the prediction of CVD. At any level of MRW at age 25 years, weight change was positively and significantly associated with CVD risk in both sexes. These results illustrate not only the detrimental effects of weight gain but also the benefits of weight reduction in obesity. The stronger relationship in men than women parallels a previously reported finding of a greater influence of weight change on risk factor change in men.[13] The present study suggests, however, that men may be more generally sensitive than women to the effects of weight change, because its impact on disease could not be attributed solely to the resulting levels of the risk factors. Although MRW at entry to the Framingham Study was a better predictor of CVD incidence than MRW at age 25 years, analyses indicate that risk was most pronounced among those who stayed in the heaviest weight class between the two time periods. These findings lend further support to the importance of duration of obesity on incidence of CVD.

The additional contribution of obesity to the long-term prediction of CVD may be its role as a precursor to the development of the major risk factors or through metabolic and physiologic mechanisms yet to be identified. It seems that the degree of obesity may, in fact, influence the later development of risk factors such as hypertension. Entry MRW in Framingham was a significant independent predictor of hypertension over 26 years in women, but not in men. Excess weight in this population may also have been associated with other lifestyle or behavioral characteristics which, over time, may have influenced CVD risk. While no data at entry were available on physical activity, diet or personality type, analyses that included an index of social class did not appear to have any impact on the relationships between weight and disease.

Other direct effects of overweight may explain its unique contribution to CVD risk. Recent data suggest that obesity is associated with fibrinolytic activity and plasma fibrinogen concentrations, which have been implicated in the onset and course of ischemic heart disease.[31] Moreover, obesity appears to increase cardiac work load and intravascular volume[32] and to alter glucose and lipid metabolism.[33] Increased cardiac work load in a heavier person may precipitate an acute event or elicit symptoms if the coronary circulation is already compromised. The burden of excess weight on the heart also has been shown in autopsy studies in which relative weight was independently related to heart size.[34, 35] Obesity has also been associated with the extent of coronary atherosclerosis at autopsy.[34]

Despite the findings from clinical and experimental studies, there is still much confusion over the complex relationship between obesity and CVD risk. Most epidemiologic studies have been concerned with the impact of overweight on coronary heart disease in men. These studies can be used to highlight some of the difficulties in interpreting and comparing results. For example, the Seven Countries Study showed no significant association between body mass index in most regions and coronary disease incidence over 10 years.[36] However, many of the populations observed were considerably leaner than the Framingham cohort, whose weights compared favorably with those in the general U.S. population.[19] The lack of sufficient heterogeneity in adiposity, and the different cultural and genetic context in which this characteristic may have operated, make comparability between these two studies difficult.

Different indexes of obesity can be differentially related to disease risk,[37] which may explain some variability in study results. While body mass index (weight/height^2) has been suggested as the preferred measure of adiposity, in Framingham it was very highly correlated with MRW (r = 0.99) and had no greater predictive power. However, skinfold measurements of subcutaneous fat accumulation correlated with MRW to a lesser degree (r = 0.40–0.65), and preliminary results suggest that these measures were associated somewhat differently with disease risk in Framingham. Furthermore, if indexes of obesity are more powerful predictors of disease in younger than older persons, differences in the age distributions of study populations may also serve to explain what appear to be conflicting results.

The length of follow-up for events in each population can also affect the conclusions drawn from various studies. Some effects of overweight may be evident only after follow-up over long periods of time, as suggested by the importance of duration of obesity on disease. Both the Framingham and Manitoba studies[1] found obesity to be an independent predictor of disease on long-term observation only. Table 4 shows how observation over different periods of time may result in different interpretations of the same data. In Framingham men, a strong and significant association between MRW and coronary disease incidence did not emerge until the 8-year follow-up, at which point the strength of the relationship remained fairly constant for

TABLE 4. *The Association Between Metropolitan Relative Weight at Entry and Coronary Heart Disease Incidence by Length of Follow-up in Framingham Men and Women*

Length of follow-up	Multivariate logistic regression coefficients for MRW	
	Men (n = 2197)	Women (n = 2714)
6 years	0.006 (114)	0.011 (56)
8 years	0.014* (154)	0.008 (78)
14 years	0.012† (314)	0.008* (166)
20 years	0.012‡ (480)	0.007* (301)
26 years	0.012‡ (636)	0.008† (437)

Regressions include adjustments for age, systolic blood pressure, serum cholesterol, cigarettes/day, glucose intolerance, and electrocardiographic left ventricular hypertrophy at exam 1.

The number of events at different follow-up times is given in parentheses.

*Coefficient is significantly different from zero, $p < 0.05$.

†Coefficient is significantly different from zero, $p < 0.01$.

‡Coefficient is significantly different from zero, $p < 0.001$.

Abbreviations: MRW = Metropolitan Relative Weight; n = number at risk.

the duration of the study. Among women, the logistic coefficients were fairly strong and consistent in all observation periods. However, statistical significance was not achieved until nearly 14 years of follow-up, for the small number of events in this group resulted in insufficient power to test assumptions. Previous analyses, based on shorter periods of observation, have suggested that there is no independent relationship between MRW and coronary risk in Framingham women.[14] These illustrations clearly show that the accumulated evidence describing the nature of the weight-disease relationship should be interpreted cautiously.

The issue of independence can be resolved only by further study, but we conclude from the existing data that leanness and avoidance of weight gain before middle age are advisable goals in the prevention of CVD for most American men and women. These data further indicate that intervention on the well-established risk factors for disease should be accompanied by weight loss in the overweight individual. Likewise, revisions to the actuarial desirable weight tables are premature, because such changes suggest that maintenance of heavier weights will not diminish health status. This assumption appears to be unsubstantiated by these as well as other data concerned with the impact of obesity on morbidity and mortality.[1, 2, 4, 18]

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